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DOCTOR OF MEDICINE

SESSION 2020-2023

TO STUDY THE ROLE OF CBNAAT IN EXTRA PULMONARY TUBERCULOSIS

(M.D.RESPIRATORY MEDICINE)

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ABBREVIATIONS

1. MTB-Mycobacterium Tuberculosis
2. WHO-World Health Organisation
3. CSF-Cerebrospinal Fluid
4. ADA-Adenosine Deaminase
5. IU/L-International Units/Litre
6. BCG-Bacilli Calmette Guerin
7. NTM-Non-Tubercular Mycobacteria
8. EPTB-Extrapulmonary Tuberculosis
9. HIV-Human Immunodeficiency Virus
10. AIDS-Acquired Immunodeficiency Syndrome
11. PTB-Pulmonary Tuberculosis
12. FIND-Foundation for Innovative New Diagnostics
13. RIF-Rifampicin
14. RRDR-Rifampicin resistance determining region
15. NAA-Nucleic Acid Amplification
16. PCR-Polymerase Chain Reaction
17. DNA-Deoxyribonucleic Acid
18. CBNAAT-Cartridge Based Nucleic Acid Amplification Test
19. MGIT-Mycobacteria growth indicator tube
20. ATT-Anti Tubercular Treatment
21. FNAC-Fine needle aspiration cytology
22. RNTCP-Revised National TB Control Programme
23. AFB-Acid Fast Bacilli

INDEX

1. INTRODUCTION ……...11
2. AIMS……14
3. OBJECTIVES……..14
4. NEED OF THE STUDY……..14
5. REVIEW OF LITERATURE……...15
6. MATERIALS AND METHODOLOGY…….20
7. FLOWCHART OF THE STUDY……21
8. SAMPLE SIZE…….22
9. DATA ENTRY AND STATISTICAL ANALYSIS……23
10. OBSERVATIONS AND RESULT……..24
11. DISCUSSION ……48
12. SUMMARY…….50
13. CONCLUSION……51
14. BIBLIOGRAPHY……52
15. INFORMED CONSENT……..….54
16. PATIENT INFORMATION SHEET……...56
17. MASTER CHART CODES…….58
18. PLAGIARISM CERTIFICATE……...63
19. MASTER CHART……...64

INTRODUCTION

Mycobacterium Tuberculosis is a complex organism in which lungs are the main portal of infection. Tuberculosis affecting organs other than lungs called as extrapulmonary tuberculosis.[1] Extrapulmonary Tuberculosis can include lymphadenitis, pleuritis, peritonitis, meningitis, ocular, oral, cutaneous, musculoskeletal, abdominal, genital, miliary tuberculosis.[1]

In low- and middle-income countries, Tuberculosis is a health problem which seeks attention.[2] It is the most common infectious disease in the world.[3] Inadequate diagnostic assays have severely hampered the ability to tackle this disease.[2]

In industrialized countries, diagnosis of extrapulmonary tuberculosis as compared to pulmonary tuberculosis is still a problem.[4]

Most severe form is the involvement of central nervous system.[1] It manifests with low grade fever, vomiting, confusion, seizures, stupor, coma.[1] CSF ADA levels 5-15IU/L indicates tubercular meningitis.[1] Molecular diagnostic tools like MTB Gene Xpert have reported 70 percent sensitivity and 97 percent specificity.[1]

Tuberculous lymphadenitis is the most common form of Extrapulmonary Tuberculosis contributing to 35 percent of Extrapulmonary Tuberculosis cases.[5] Cervical lymph nodes are most commonly involved, others like axillary, mediastinal, mesenteric, inguinal lymph nodes are also involved.[5]

It is challenging to diagnose tubercular lymphadenitis as fine needle aspiration cytology does not differentiate between tuberculosis and non-tubercular mycobacteria. The major causative agents of Tuberculosis lymphadenitis are Mycobacterium Tuberculosis and Mycobacterium Bovis.[5] Several conditions like fungal infections and sarcoidosis can have the same cytological picture.[6]

The most common cause of pleural effusion in India is tuberculosis.[6]ADA greater than 40U/L is often considered as Tubercular pleural effusion in India, but in order to make definitive diagnosis we need to demonstrate granulomas in the pleural tissue which often lacks sensitivity.[5]

AFB smear has little role in the diagnosis of Extrapulmonary tuberculosis.[7]Fine needle aspiration cytology, is a simple and rapid technique but lacks specificity.[8] In both smear microscopy and fine

needle aspiration cytology there is no detection of drug resistance and have limitation in species identification.[8]

The Tuberculin Sensitivity Test yields false positive results due to BCG vaccination or sensitization with NTM. The concept for extrapulmonary tuberculosis still remains novel for people who present to the physician and get diagnosed with EPTB yet refuse to believe often claiming that they don't have any chest symptoms.[9]

There is another misconception regarding EPTB that it manifests in people who are immunocompromised like HIV, AIDS, organ transplant patients.[9] Recent studies show a gradual increase in the proportion of patients with EPTB in comparison with PTB in normal population.[9]The burden of TB cases in India is higher so a proportionate higher number of EPTB cases are observed in India.[10] Extrapulmonary tuberculosis remains undiagnosed for a longer time in a majority of cases.[11] Diagnosis of Extrapulmonary Tuberculosis remains challenging due to its paucibacillary nature.[2]

A major hinderance in the diagnosis of EPTB is its atypical nature and often simulates neoplasia.[4] Owing to the cumbersome and slow conventional methods, FIND(Foundation of Innovative and New Diagnostics) introduced Cartridge based nucleic acid amplification assay which is a molecular method which detects MTB as well as RIF resistance which is surrogate marker of MDR-TB which confers mutations in 81bp RIF resistance determining region(RRDR) of the rpoB gene coding for the beta subunit of RNA polymerase of MTB which is the genetic basis for RIF resistance.[11] When prevention and treatment is a top priority for decreasing the number of Tuberculosis cases, prompt and accurate diagnosis is necessary.[12]

NAA tests such as PCR detects nucleotide sequences which is unique to Mycobacterium Tuberculosis directly in specimens from extrapulmonary sites have greater accuracy and speed than AFB smear microscopy which gives results within few hours.[5] Viable and non-viable organisms cannot be differentiated by DNA-PCR while mRNA is more prone to destruction as compared to genomic DNA, so a positive mRNA signals the presence of viable organisms.[5] Tests like CBNAAT and pleural biopsies are reserved for patients with borderline ADA to diagnose Tubercular Pleural Effusion.[13]

Heminested real time PCR is used by the Xpert assay to amplify Mycobacterium specific rpoB gene. The rifampin resistance determining region of the rpoB gene is probed with molecular beacons to determine rifampin resistance. This assay runs on GeneXpert platform in a nearly fully automated

manner, including bacterial lysis, nucleic acid extraction and amplification, and amplicon detection.[14]

There is a shift in the management of Tuberculosis with Gene Xpert assay.[13] This is a rapid, semi quantitative nucleic acid amplification test which has an important and definite role in the work up and diagnosis of Pulmonary and EPTB.[13] Role of CBNAAT in the diagnosis of tubercular pleural effusion remains unclear. [13]

CBNAAT is a cartridge based nucleic acid amplification test which detects the presence of Mycobacterium Tuberculosis as well as Rifampicin resistance.[7] It is a cost effective and rapid test, which may revolutionize the diagnosis of Extrapulmonary Tuberculosis. [7] In India, Trunaat is a novel, cost effective and rapid method of detecting Mycobacterium Tuberculosis in clinical samples which is a point of care, battery operated and chip based RTPCR micro device and Rifampicin resistance can be detected with a second chip as a follow-on test.[15]

Finding of Tubercle on histopathological examination is the most reliable method of diagnosis-consisting of lymphocytes, epithelioid cells, macrophages and giant cells with central caseation necrosis.[9]

PCR based MGIT 960 liquid media is able to detect Mycobacterium Tuberculosis growth faster (5-10 days) when compared with Lowenstein Jensen media.[12]

As per WHO, EPTB should be diagnosed on the basis of culture positive specimen or caseating granuloma on biopsy or strong clinical evidence consistent with active Extrapulmonary Tuberculosis. [16]

AIM

To Study the role of CBNAAT in diagnosis of Extrapulmonary tuberculosis.

OBJECTIVES

1. To calculate the yield of CBNAAT in EPTB.

2.To compare the diagnostic efficacy of CBNAAT and AFB culture in the diagnosis of all forms of EPTB.

NEED OF STUDY

- Compare the yield of CBNAAT and AFB culture.
- Gives faster result comparative to culture. so, that ATT can be initiated as soon as possible.
- Rifampicin resistance helps to treat drug resistance and to start appropriate ATT.

REVIEW OF LITERATURE

Singh KG et al did a prospective study in the age group 10-80 years, who were suspected cases of tubercular peripheral lymphadenopathy, at people's hospital, Bhopal over a period of one year six months. FNA of peripheral lymph nodes of 57 patients were sent for cytology and CBNAAT. Study showed statistical significance in the diagnostic yield of FNAC that is 82.4 % and CBNAAT that is 77.9% in tubercular peripheral lymph nodes.[1]

Shamma Shetye et al conducted a study in the department of Molecular Biology, Metropolis Healthcare, Mumbai where suspected cases of EPTB were included in the study and were subjected for CBNAAT. Extrapulmonary samples included pus and aspirates, body fluid, pleural fluid, lymph node tissue and others. 81.89% cases were detected as MTB negative and RIF negative. 2.73% cases were detected to have MTB positive and RIF positive of which maximum cases i.e., 40.38% were observed in pus and aspirates, followed by body fluids which accounted for 25.03%, followed by pleural fluid which accounted for 12.50% and lymph nodes accounted for 10.57%.

In cases which were MTB positive and Rifampicin negative, positivity rate of CBNAAT was around15.37%, the maximum cases were observed in pus and aspirates with 49.74%, followed by body fluids with 17.09%, lymph node tissue accounted for 11.11% and pleural fluids accounted for 9.57%.[3]

E. Tortoli et al conducted a study in 2012 where extrapulmonary samples like biopsies, pleural fluids, gastric aspirates were included in the study. All the specimens were subjected for acid fast microscopy and culture in both solid and liquid media. Xpert test was applied on the samples for which at least 0.5 ml of the concentrates were available and Xpert results were compared with the culture results. In 128 culture positive samples, acid fast bacilli were detected microscopy and growth of mycobacteria was obtained on culture in 183 smear negative samples. When compared with Xpert, sensitivity of microscopy was 48 percent and when compared with culture, sensitivity of smear microscopy was 47 percent. Overall sensitivity and specificity of Xpert were 70 percent and 97.3 percent which went on to 81.3 percent and 99.8 percent after sorting out the discrepancies.[4]

Yadav. K and Veena. M conducted a study from the year 2016 to 2018 at Bangalore Medical College in which 281 clinically suspected EPTB patients were received in RNTCP lab from various departments of their hospital and private hospitals.

Details of the cases in terms of demographic data, HIV status and treatment received were noted down.

Extrapulmonary samples were collected in terms of pus, aspirates, body fluids and lymph node tissues were collected in special, plain, universal container that is falcon tube under aseptic conditions.

5 ml of the samples were received to which buffer solution was added, then the mixture was loaded to cartridge which were processed by Gene Xpert assay.

In the study 58.7% were males and 41.2% were females.

73(25.97%) were FNAC,115 (40.925) were pleural fluid,36(12.8%) was ascitic fluid,22 (7.82%) was csf,9(3.2%) were aspirates.

In this study 23.8% were CBNAAT positive and one patient was MTB positive rifampicin resistant.

Maximum MTB positives were found in FNAC (52.2%).[11]

Elizabeth Bahar. et al conducted a study in 2019 in which suspected cases of extrapulmonary tuberculosis were taken in the study where 20 samples of pleural fluid samples were taken and 2 out of 20 were positive for AFB stain and 18 out of 20 were negative for AFB stain. 10 samples of cerebrospinal fluids were taken into the study, 10 out of 10 were negative for AFB stain and 2 samples of abscess were taken into the study, 2 out of 2 were negative.[12]

Radha Gopalswamy. et al updated on the diagnosis and treatment of extrapulmonary tuberculosis and drug resistance. Extrapulmonary tuberculosis can also be caused by Mycobacterium Tuberculosis complex. Extrapulmonary Tuberculosis can occur through dissemination from primary source like Pulmonary Tuberculosis, through hematogenous route, lymphatic route or localized bacillary dissemination. It can be tuberculosis of the brain, eye, mouth, peritoneum, lymph nodes of neck, spine, bones, muscles, skin, pleura, pericardium and gastrointestinal system. Diagnosis of extrapulmonary tuberculosis can be made by clinical, radiological, microbiological, histopathological, biochemical and by immunological and molecular methods. However, to differentiate between mycobacterium tuberculosis complex and non-tubercular mycobacteria, culture and molecular techniques are considered confirmatory.[2]

Catharina C. Boehme. et al conducted a study on Rapid Molecular Detection of Tuberculosis and Rifampicin Resistance where 1843 patients were screened which constituted subjects who were tubercular suspects, therapy failure, retreatment, or contact with multidrug resistant patients, out of which 1730 patients were eligible for three sputum sample collection, out of which 268 were excluded and 1462 subjects were included in the main analysis.741 subjects were culture positive

and 721 were culture negative. Out of 741 culture positive, 567 were smear positive and smear negative. Out of 721 culture negative subjects, 105 had clinical tuberculosis and 616 did not have tuberculosis. The overall sensitivity of CBNAAT test among culture positive tuberculosis was 97.6%. Sensitivity for smear positive and culture positive cases was 99.8% and for smear negative and culture positive cases was 90.2%.[17]

M. Kashif Munir, Iffat Shabbir, Rizwan Iqbal, Saulat Ullah Khan conducted a study in 2007 and compared AFB smear and Mycobacterial culture from specimens received for the diagnosis of Extrapulmonary Tuberculosis in which 271 specimens from patients suspected to have Extrapulmonary Tuberculosis were taken. The clinical specimens were subjected for direct and concentrated smears and were stained with ZN stain. The clinical specimens were also subjected for culture in Lowenstein Jensen media. Taking Mycobacterial culture as the gold standard, sensitivity, specificity, positive predictive value and negative predictive value were calculated for AFB smear microscopy. Out of 271 extrapulmonary samples processed for AFB smear and culture, 11 got contaminated and were excluded from the study. Remaining 260 specimens which were tested for smear and culture,10 was smear positive that is 3.85% and 48 were culture positive that is 18.46 percent. The sensitivity of AFB smear microscopy for extrapulmonary specimen was 20.84 percent and specificity were 100%.[18]

Doris Hilleman et.al conducted a study in which 521 extrapulmonary samples were sent to the National Reference Centre for Mycobacteria between May 2009 and August 2010.Of 521 samples,245 were tissue samples in which lymph node contributes for the maximum.62 out of 521 came out to be positive for culture out of which 6 smear positive for acid fast bacilli. In comparison of CBNAAT with culture method, 501 specimens were interpretable and 20 samples were excluded from further study. The sensitivity was 77.3% whereas the specificity is 98.2% respectively. Out of 245 tissue samples, 29 were culture positive and Xpert assay detected 20 out of 29 positives for culture.[14]

Soumitesh Chakravorty, Manas Kamal Sen et al conducted a study at department of Respiratory Medicine, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi where ninety-nine extrapulmonary samples which included pleural fluid, pleural tissues and lymph node tissues were collected from eighty-seven. Patients were enrolled in the study between October 2002 and January 2003.All the cultures came out to be positive whereas the overall sensitivity of smear microscopy was 21.1%. The sensitivity of PCR assays ranged between 66.7% and 83% and specificity ranged between 75% and 100%.[6]

Anushree Chakraborty, Swapna Ramaswamy et al conducted a study in 2019 in which 75 cases of pleural effusion were enrolled for the study. After functional status assessment, diagnostic thoracocentesis was performed and pleural fluid was sent for CBNAAT and various other cytological, biochemical and microbiological analysis. All the 75 patients had a complete resolution of effusion after initiation of ATT.

CBNAAT was positive for mycobacterium tuberculosis in 32% of the subjects.[13]

Shiv prasad Kasat, Mahendra Biradar, Ashish Deshmukh et al conducted a study on Effectiveness of CBNAAT in the diagnosis of extrapulmonary tuberculosis in 2018 where people with pulmonary tuberculosis and age below 18 years were excluded from the study. Patients with clinical suspicion of extrapulmonary tuberculosis were enrolled in the study. Samples were collected from the extrapulmonary sites and were subjected to AFB smear and CBNAAT.

Samples collected were lymph node aspirate, pleural fluid, ascitic fluid, pus, colonic fluid, synovial fluid, urine. Among 166 clinical suspects, 17 cases came out to be smear positive for AFB and 149 cases were found to be smear negative for AFB. 25 out of 166 clinical suspects came out to be positive for mycobacterium tuberculosis in CBNAAT and 141 were negative for the same.[7]

Sunil Kumar komanapalli et al did an observational study at Andhra Medical College, Vishakhapatnam over a period of 12 months with a sample size of 289 cases.

Presumptive cases of EPTB, purulent aspirates on FNA from various sites between the age group 1 to 60 years were taken.

FNAC specimens were collected and smears were prepared for cytology for Hematoxylin and Eosin staining and was evaluated under LED microscopy.

Out of 289 cases, cytomorphological features consistent with tuberculosis were 51.04%, CBNAAT diagnosed 49.1% of the cases and led detected 39.7% of the cases.

94.1%of the cases were aspirated from cervical lymph nodes out of which 50.7% of the cases were positive for CBNAAT.

161 out of 289 cases were purulent aspirates, out of which 100 cases that is 62.1% cases were CBNAAT positive.

In 50.5% of the cases of tuberculous lymphadenitis,84.34% of cases were CBNAAT positive.

Diagnostic performance of cbnaat in terms of sensitivity, specificity, positive likelihood ratio, negative likelihood ratio was 85.71%,96.87%,21.21 and 0.15 respectively.[8]

Reena Anie Jose, Krishna Gopal et al conducted a study from January 2019 to December 2019 in which 248 cases were enrolled in the study. All clinically suspected cases of extrapulmonary tuberculosis which included Pleural TB, Abdominal TB, Lymph node TB, Pericardial TB, Spinal TB, Genitourinary TB, Cutaneous TB, Bone and joint TB were included in the study. Out of 248 samples tested for CBNAAT 9 (3.6%) came out to be positive for MTB. The predominant type of extrapulmonary tuberculosis in this study was lymph node tuberculosis.[15]

Ganji R et al conducted a study over a period of 4 years from January 2015 to December 2018 where clinically suspected cases of extrapulmonary tuberculosis were enrolled in the study in which patients with clinical features of lymph nodal, synovial disease, with non-healing skin sinus, neurological impairment and clinical features suggestive of Pott's spine, abdominal tuberculosis was included in the study. Overall, it was found that CBNAAT was better at diagnosing extrapulmonary tuberculosis as compared to cytology(p=0.01), AFB smear and AFB culture (0.008). CBNAAT and cytology were significantly better at diagnosing lymph node tuberculosis and CBNAAT was significantly better at diagnosing spinal tuberculosis than AFB on microscopy.[9]

MATERIALS AND METHODOLOGY

STUDY DESIGN: - Cross Sectional Study

PLACE OF STUDY: - Department of Respiratory Medicine, Santosh Hospital, Ghaziabad, (U.P)

STUDY POPULATION: - Clinically suspected cases of extrapulmonary tuberculosis both inpatient and outpatient were enrolled in the study after their consent. The samples included Lymph node aspirate, Pleural Fluid, Ascitic Fluid, Cerebrospinal Fluid and Abscess

DURATION OF STUDY: - One year study

SAMPLE SIZE: - sample size is 89.

INCLUSION CRITERION: -

1.All adult patients (>18years) suspected of Extrapulmonary tuberculosis which includes Superficial Lymphadenitis, Pleural effusion, Abdominal Kochs, Cerebrospinal Fluid and Abscess.

2.All genders.

3.All new as well as retreatment EPTB cases.

EXCLUSION CRITERION:

1.Extrapulmonary samples contaminated with blood, stool, blood

2.Pleural Effusion due to Chronic Renal Failure and Cardiac Failure

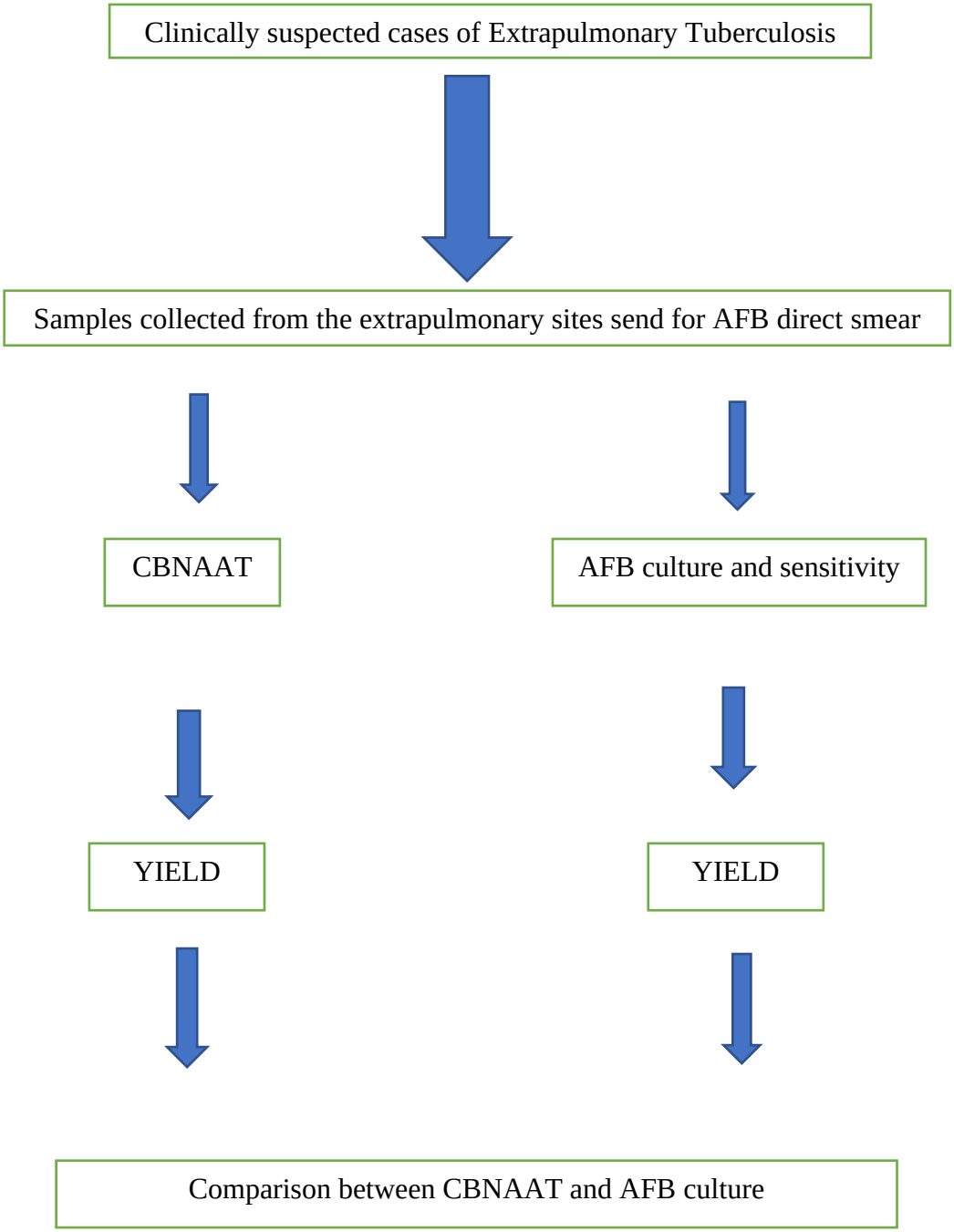
It is a Cross sectional study conducted at Santosh Hospital, Ghaziabad where all the clinically suspected cases of Extrapulmonary tuberculosis were taken in the study.

Samples were collected from the appropriate extrapulmonary sites which included Lymph Node aspirate, Pleural fluid, Ascitic fluid, Abscess, Cerebrospinal Fluid

The samples were sent for AFB smear, CBNAAT and AFB culture.

The data was analyzed and results were compared.

FLOW CHART OF THE STUDY


Clinically suspected cases of Extrapulmonary Tuberculosis
Samples collected from the extrapulmonary sites send for AFB direct smear
CBNAAT
AFB culture and sensitivity
YIELD
YIELD
Comparison between CBNAAT and AFB culture

SAMPLE SIZE:

$$n = Z^2_{1\text{-ALPHA}/2\ P}(1\text{-}P)/l^2$$

Where,

Z= 1.96 at 5% level of significance

P = Prevalence of lymph nodes 52.2%

L = Relative error that is 20% of P.

Sample size 89

DATA ENTRY AND STATISTICAL ANALYSIS:

The collected data were transformed into variables, coded and entered in Microsoft Excel. Data were analysed and statistically evaluated using SPSS-PC-25 version.

Quantitative data was expressed in mean± standard deviation. Qualitative data were expressed in frequency and percentage and statistical differences between the proportions were tested by chi square test or Fisher's exact test. Agreement between CBNAAT and AFB culture was assessed by Kappa agreement. Sensitivity, specificity, positive predictive and negative predictive value of CBNAAT was calculated. P' value less than 0.05 was considered statistically significant.

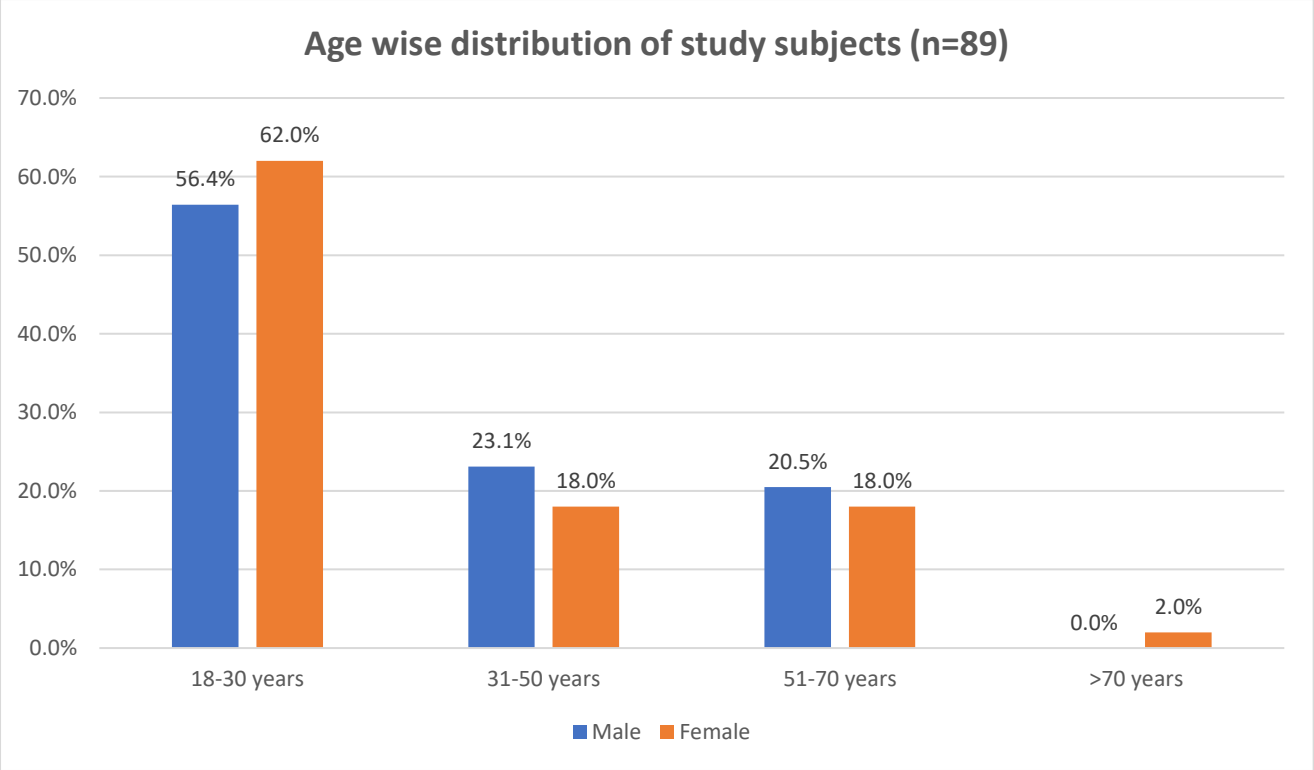
OBSERVATIONS & RESULTS

1. Various parameters of the study and its association with EPTB

Table 1: Age wise distribution of study subjects (n=89)

Age group	Male	Female	Total
18-30 years	22 (56.4%)	31 (62%)	53 (59.6%)
31-50 years	9 (23.1%)	9 (18%)	18 (20.2%)
51-70 years	8 (20.5%)	9 (18%)	17 (19.1%)
>70 years	0	1 (2%)	1 (1.1%)
Total	39 (43.8%)	50 (56.2%)	89

Figure 1



As seen from Table 1 and Fig 1, out of 89 cases, there were 22(56%) males and 31(62%) females between 18-30 years of age, 9 (23%) males and 9 (18%) females between 31-50 years of age, 8 (20.5%) males and 9 (18%) females between 51-70 years of age,1 (2%) female greater than 70 years of age.

Clinical parameter

Table 2: Type of EPTB in study subjects (n=89)

Type of EPTB	No.	%
Tubercular lymphadenopathy	57	64.0
Tubercular pleural effusion	22	24.7
Tubercular ascites	4	4.5
Tubercular abscess	5	5.6
Tubercular meningitis	1	1.1

Figure 2

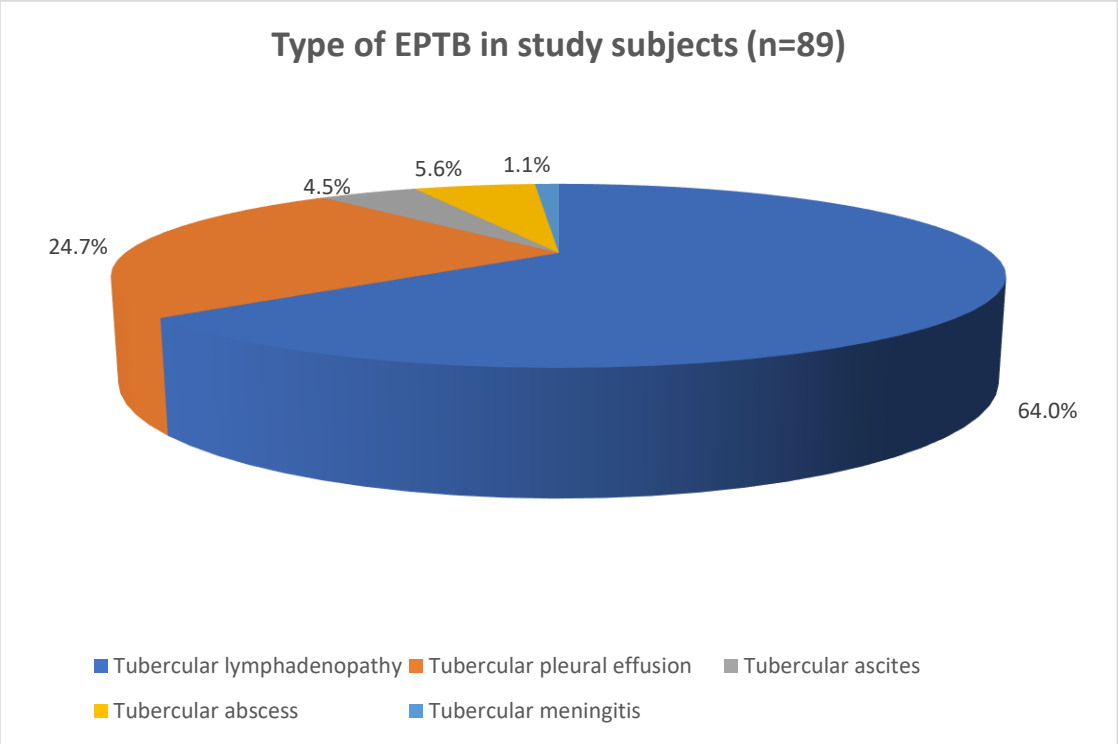
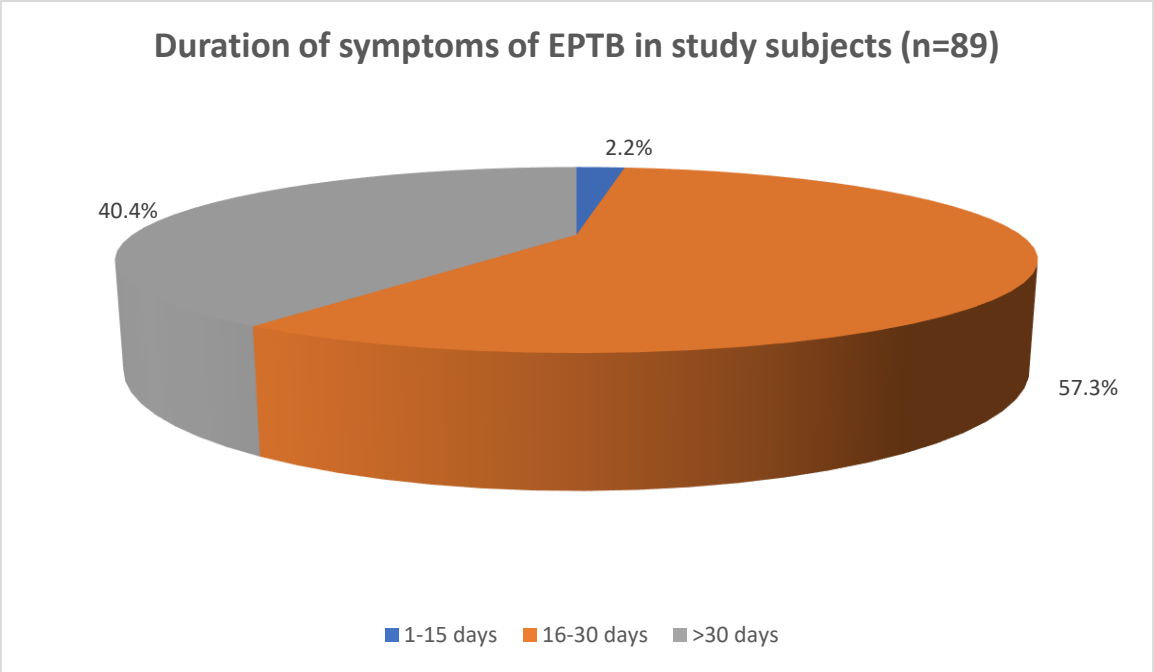


Table 2 and Fig 2 depicts, out of 89 cases, 57(64%) were tubercular lymphadenopathy, 22(24.7%) were tubercular pleural effusion, 4(4.5%) were tubercular ascites, 5(5.6%) were tubercular abscess, 1(1.1) was tubercular meningitis

Table 3: Duration of symptoms of EPTB in study subjects (n=89)

Duration of symptoms of EPTB	No.	%
1-15 days	2	2.2
16-30 days	51	57.3
>30 days	36	40.4

Figure 3

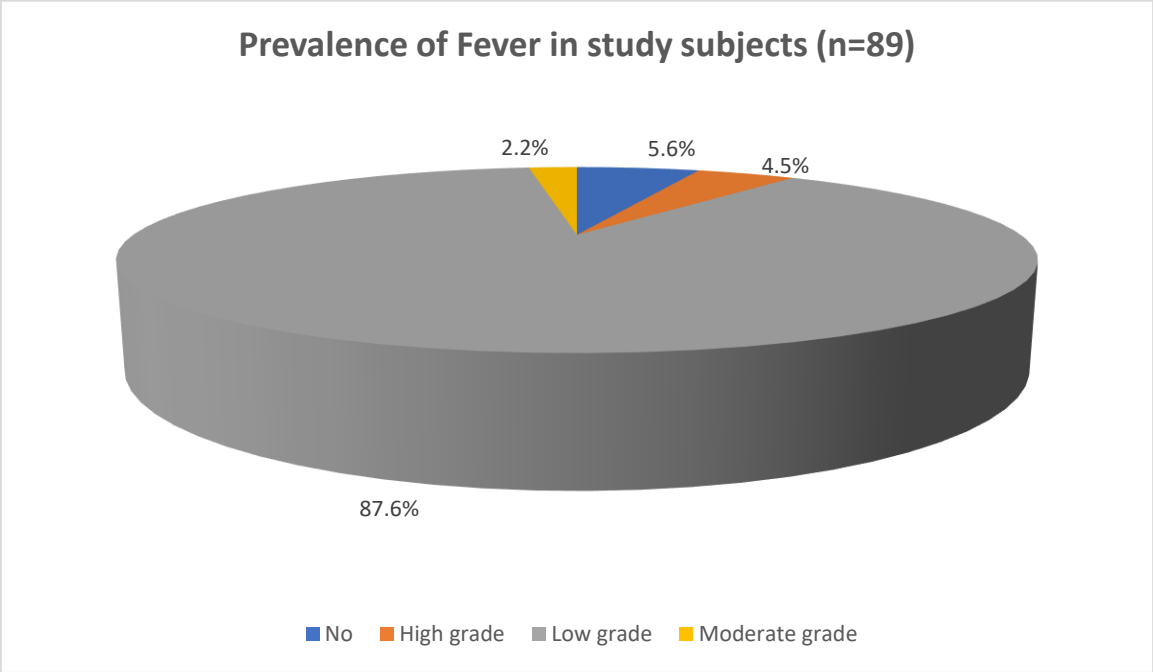


As observed from Table 3 and Fig 3, out of 89 cases, 2(2.2%) cases had duration of symptoms of extrapulmonary tuberculosis for 1-15 days, 51(57.3%) cases had duration of symptoms of extrapulmonary tuberculosis for 16-30 days, 36(40.4%) had duration of symptoms for greater than 30 days.

Table 4: Prevalence of Fever in study subjects (n=89)

Fever	No.	%
No	5	5.6
High grade	4	4.5
Low grade	78	87.6
Moderate grade	2	2.2

Figure 4



As seen from Table 4 and Fig 4, out of 89 cases, 5(5.6%) cases had no fever, 4(4.5%) cases had high grade fever, 78(87.6%) cases had low grade fever and 2(2.2%) cases had moderate grade fever.

Table 5: Prevalence of systemic symptoms in study subjects (n=89)

Other symptoms	No.	%
Loss of appetite	85	95.5
Loss of weight	85	95.5

Figure 5

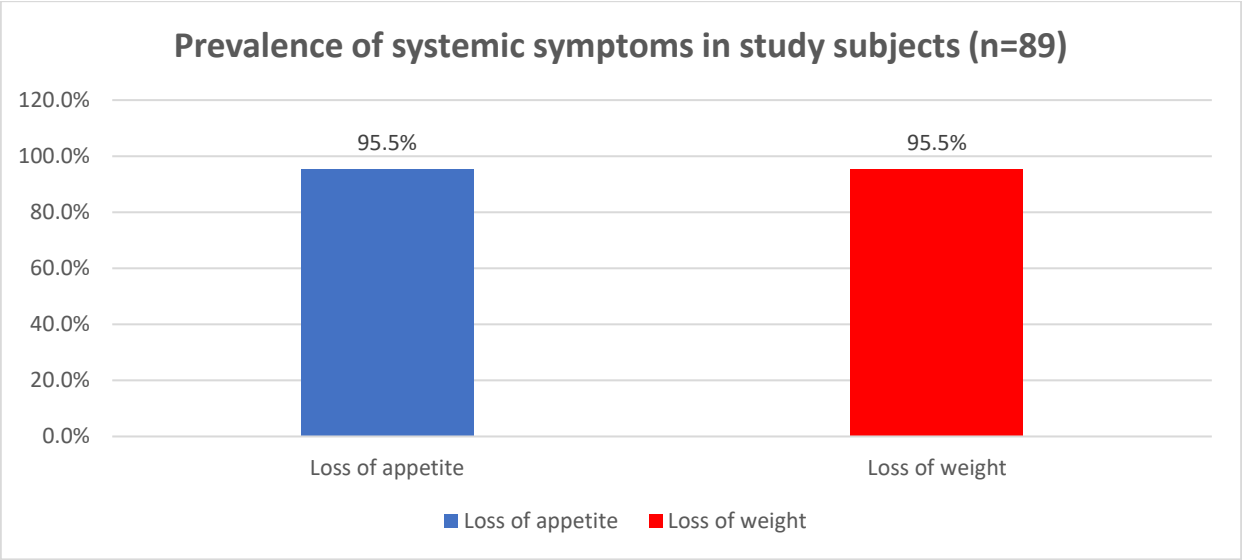
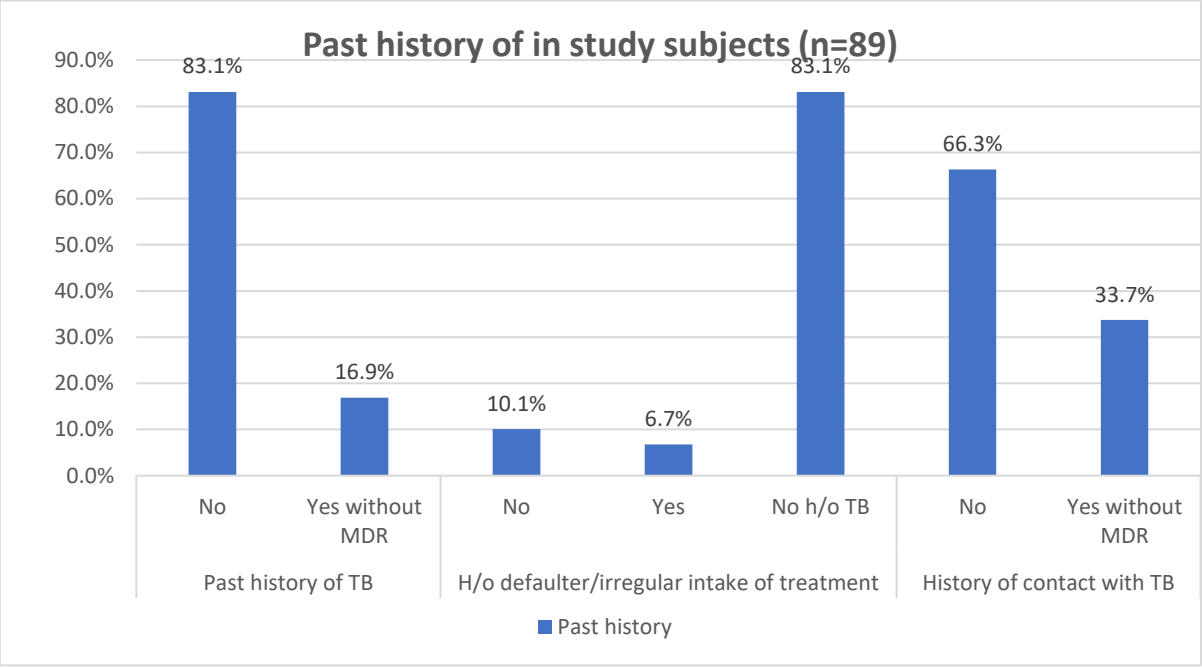


Table 5 and Fig 5 shows out of 89 cases, 85(95.5%) had loss of appetite and 85(95.5%) had loss of weight.

Table 6: Past history of Tuberculosis in study subjects (n=89)

Past history	No.	%
Past history of TB		
No	74	83.1
Yes, without MDR	15	16.9
H/o defaulter/irregular intake of treatment		
No	9	10.1
Yes	6	6.7
No h/o TB	74	83.1
History of contact with TB		
No	59	66.3
Yes without MDR	30	33.7

Figure 6

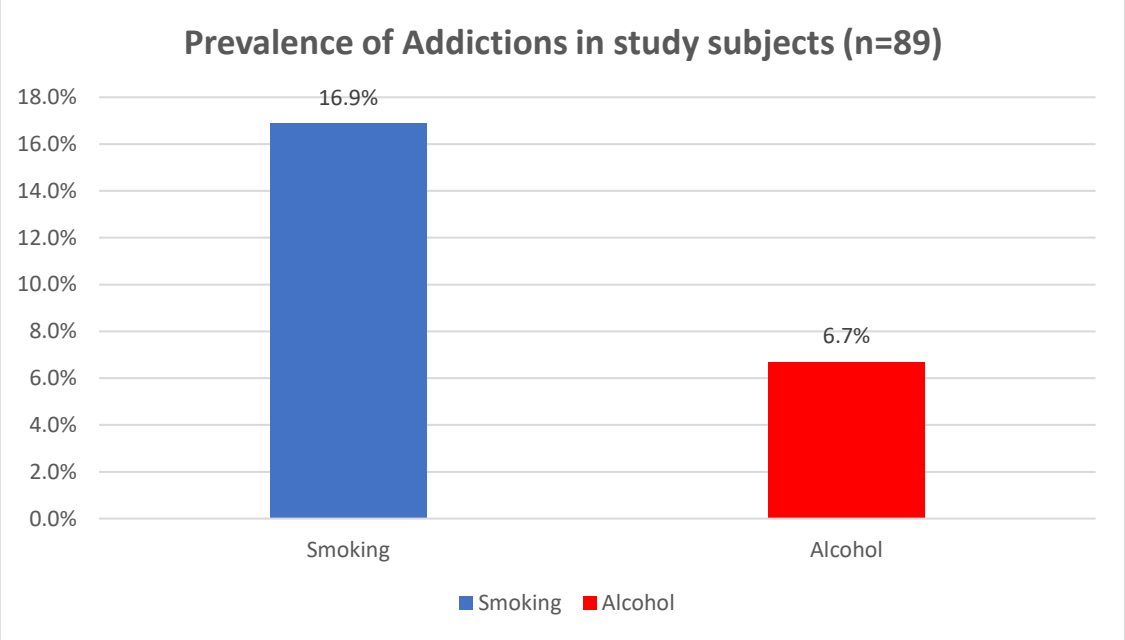


As shown in Table 6 and Fig 6, out of 89 cases, 74(83.1%) had no past history of tuberculosis and 15(16.9%) had past history of tuberculosis without MDR, 9(10.1%) had no history of default/irregular intake of ATT, 6(6.7%) had history of default/irregular intake and 74(83.1%) had no history of tuberculosis, 59(66.3%) had no history of contact with tuberculosis and 30(33.7%) had history of contact with tuberculosis but without MDR.

Table 7: Prevalence of Addictions in study subjects (n=89)

Personal history	No.	%
Smoking	15	16.9
Alcohol	6	6.7

Figure 7



As seen from Table 7 and Fig 7, out of 89 cases, 15(16.9%) had a history of smoking and 6(6.7%) had history of alcohol intake.

Table 8: Prevalence of Common Comorbidities in study subjects (n=89)

Comorbidities	No.	%
DM	14	15.7
HIV	1	1.1

Figure 8

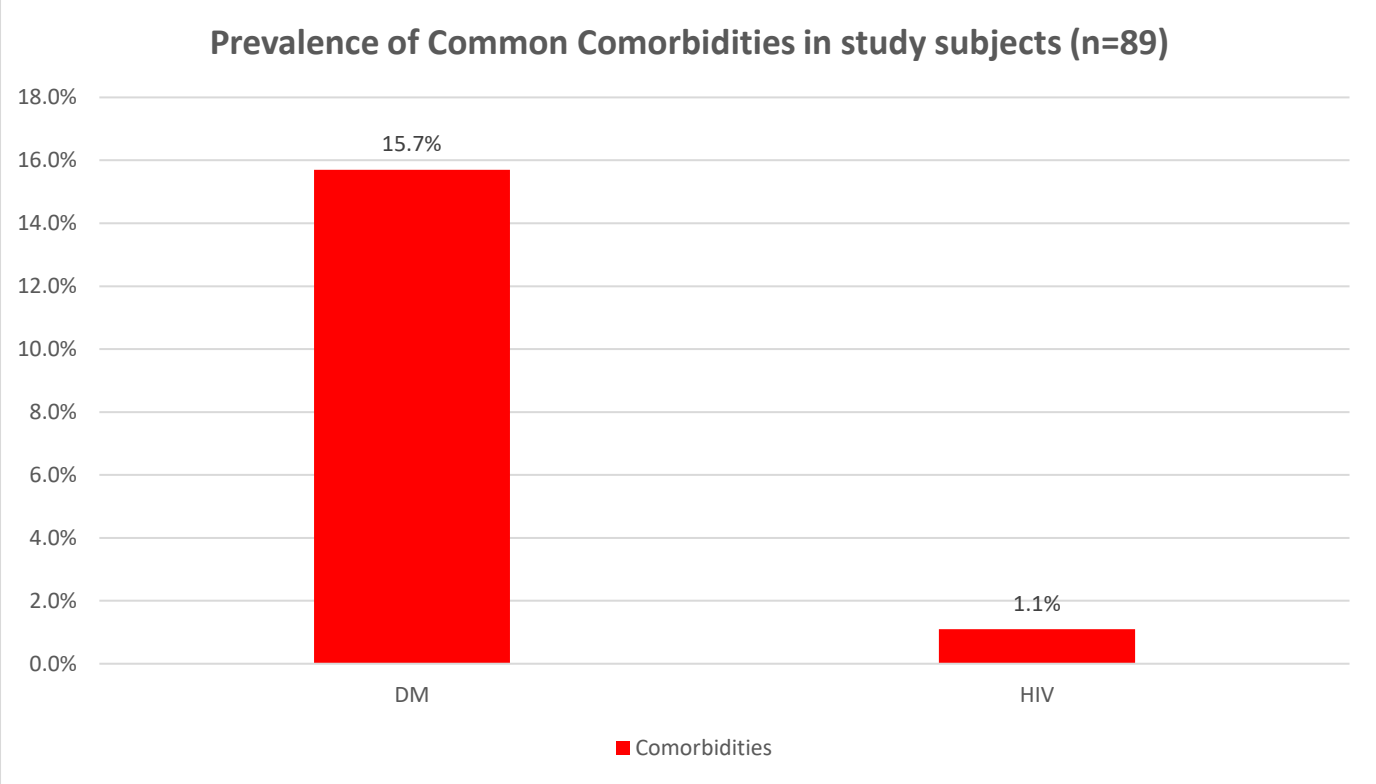


Table 8 and Fig 8 shows 15(15.7%) had a history of type 2 diabetes mellitus and 1(1.1%) had a history of PLHIV.

Table 9: GPE finding in study subjects (n=89)

GPE finding	No.	%
Pallor	7	7.9
Icterus	0	0.0
Clubbing	0	0.0
Cyanosis	0	0.0
Lymphadenopathy	56	62.9
Oedema	7	7.9

Figure 9

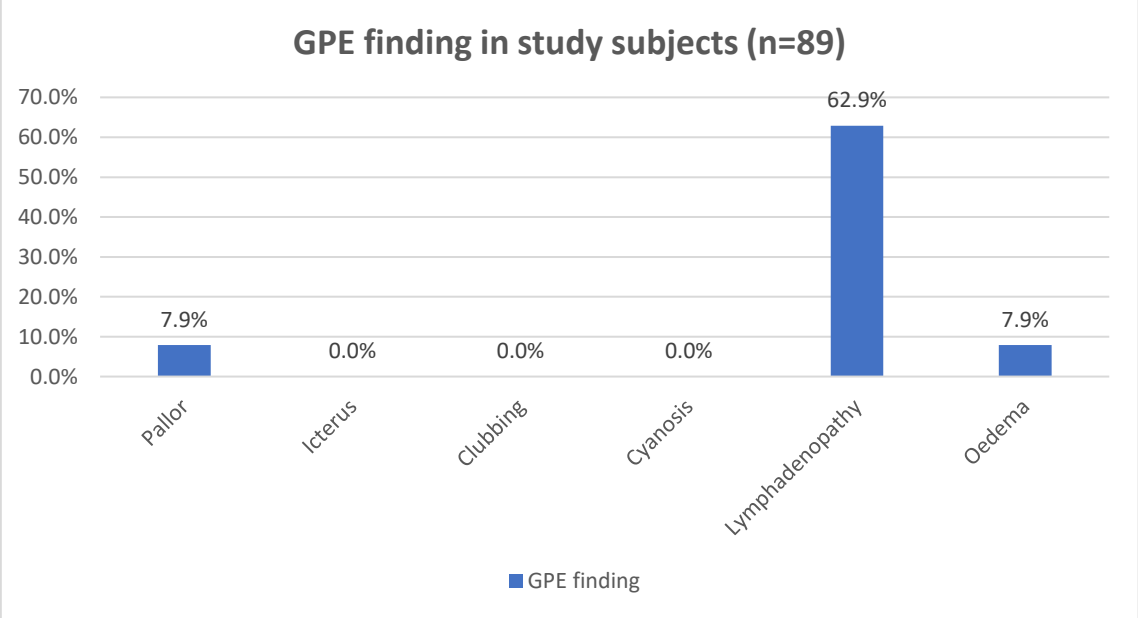
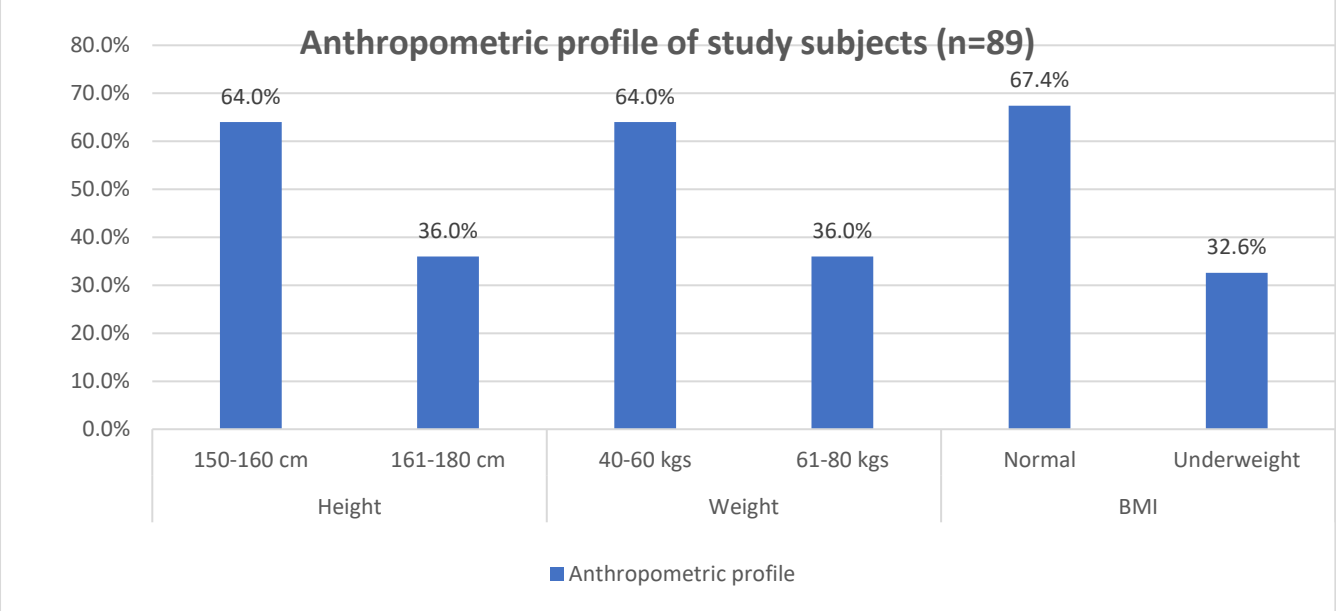


Table 9 and Fig 9 depicts out of 89 cases, 7(7.7%) had pallor and 7(7.7%) had edema in General Physical Examination.

Table 10: Anthropometric profile of study subjects (n=89)

Anthropometric profile	No.	%
Height		
150-160 cm	57	64.0
161-180 cm	32	36.0
Weight		
40-60 kgs	57	64.0
61-80 kgs	32	36.0
BMI		
Normal	60	67.4
Underweight	29	32.6

Figure 10

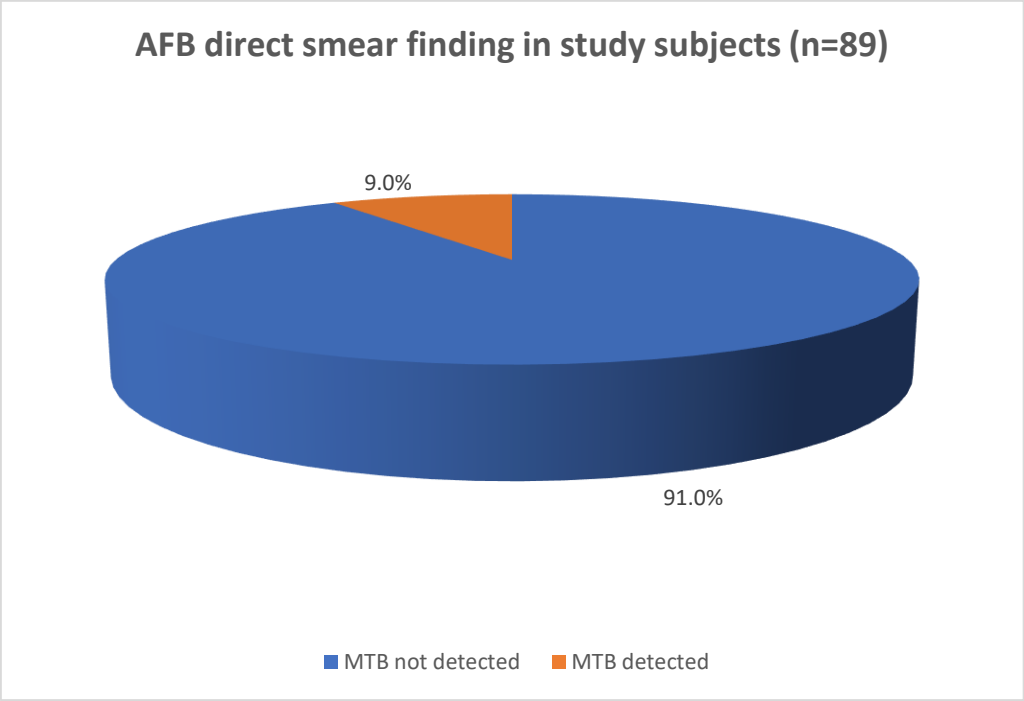


As depicted in Table 10 and Fig 10, out of 89 cases, height of 57(64%) cases were between 150-160cm and height of 32(36%) cases were between 161-180cm, weight of 57(64%) were between 40-60kgs and weight of 32(36%) were between 61-80kgs, BMI of 60(67.4%) were in the normal range 29(32.6%) cases were underweight.

Table 11: AFB direct smear finding in study subjects (n=89)

AFB direct smear	No.	%
MTB not detected	81	91.0
MTB detected	8	9.0

Figure 11

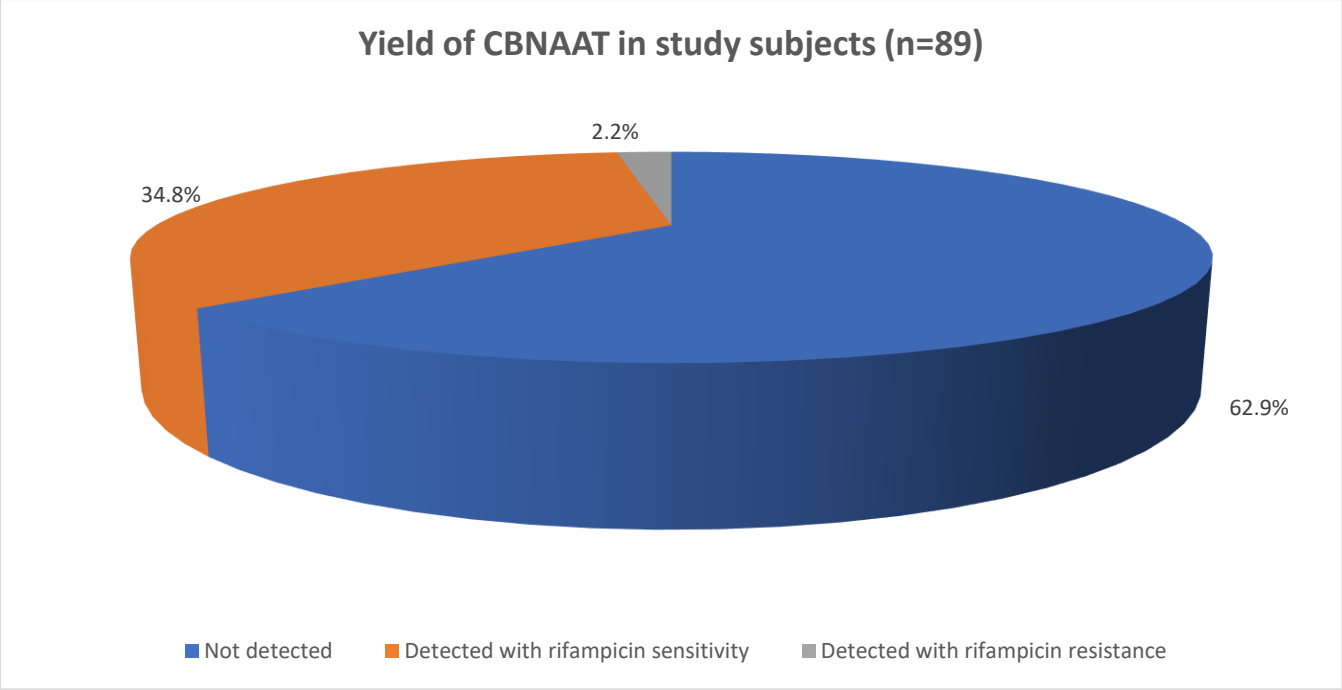


As shown in the Table 11 and Fig 11, out of 89 cases, 81(91%) cases were not detected with MTB and 8(9%) cases were detected with MTB on AFB direct smear.

Table 12: Yield of CBNAAT in study subjects (n=89)

CBNAAT	No.	%
Not detected	56	62.9
Detected with rifampicin sensitivity	31	34.8
Detected with rifampicin resistance	2	2.2

Figure 12

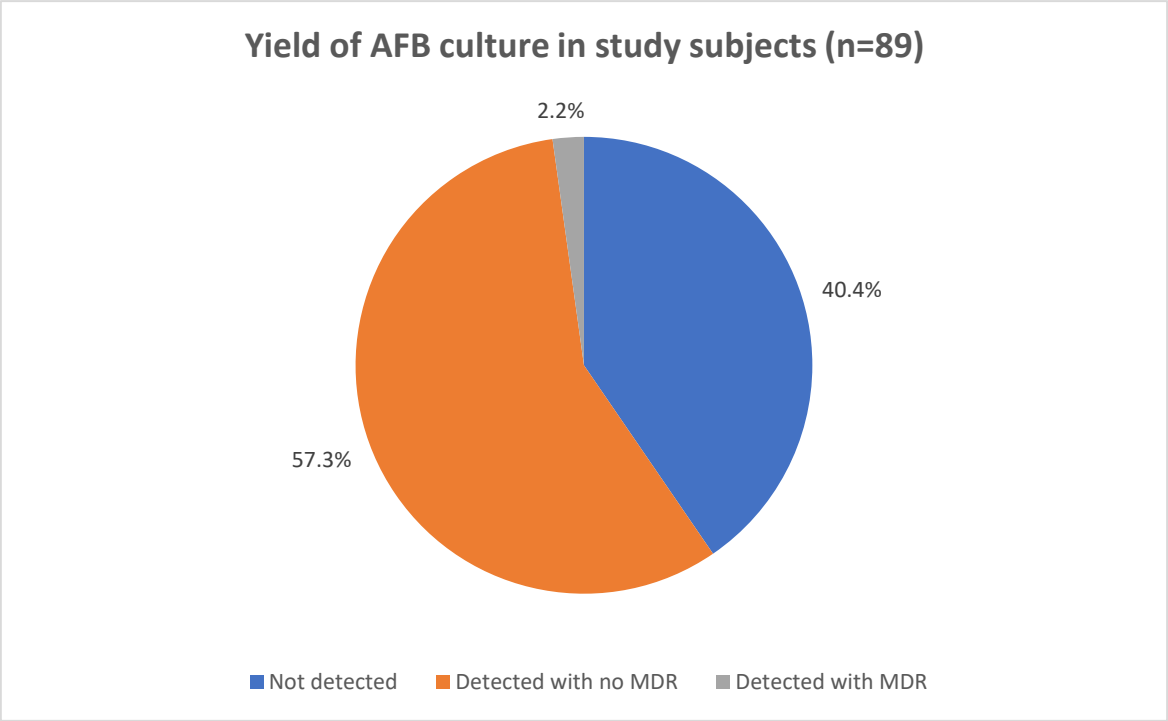


As observed from the above Table 12 and Fig 12, out of 89 cases, MTB was not detected in CBNAAT in 56(62.9%) cases and MTB was detected in CBNAAT in 33(37%) cases giving a Yield of 37% with RIF resistance in 2(2.2%) cases.

Table 13: Yield of AFB culture in study subjects (n=89)

AFB culture	No.	%
Not detected	36	40.4
Detected with no MDR	51	57.3
Detected with MDR	2	2.2

Figure 13



As shown in the above Table 13 and Fig 13, out of 89 cases, MTB was not detected in 36(40.4%) in AFB culture and MTB was detected in 53(59.5%) giving it a yield of 59.5% in which 2(2.2%) were detected to have MDR.

2. Distribution of various parameters with respect to different types of EPTB

Table 14: Age wise distribution of different type of EPTB (n=89)

Age group	TB lymph node (n=57)	TB pleural effusion (n=22)	Others (n=10)
18-30 years	1 (1.8%)	4 (18.2%)	0
31-50 years	1 (1.8%)	0	3 (30%)
51-70 years	54 (94.7%)	17 (77.3%)	7 (70%)
>70 years	1 (1.8%)	1 (4.5%)	0

Figure 14

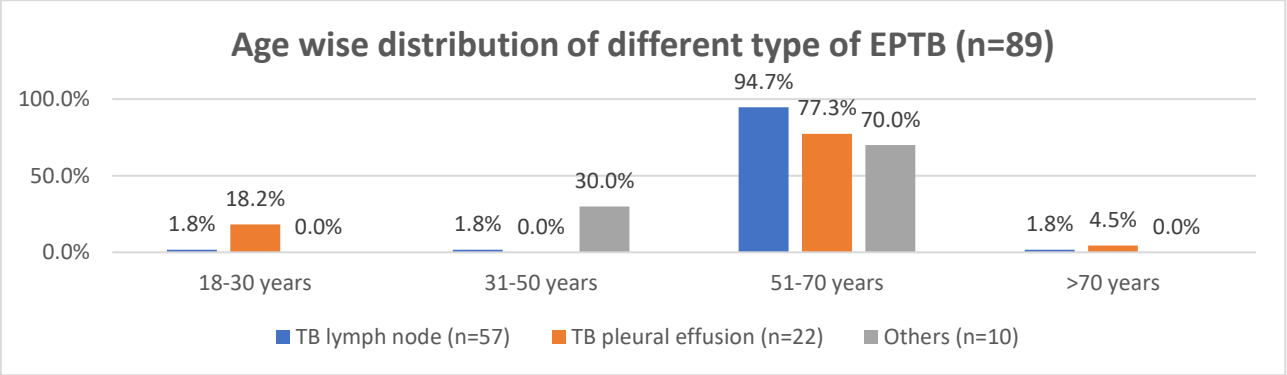


Table 14 and Fig 14 shows out of 89 cases, 1(1.8%) lymph node tuberculosis cases, 4(18.2%) cases of tubercular pleural effusion were between 18-30years of age, 1(1.8%)lymph node tuberculosis cases and 4(30%) of other forms of tuberculosis were between 31-50 years of age, 54(94.7%) lymph node tuberculosis, 17(77.3%) tubercular pleural effusion and 7(70%) other form of tuberculosis were between 51-70 years of age, 1(1.8%) lymph node tuberculosis and 1(4.5%) tubercular pleural effusion were above 70 years of age.

Table 15: Gender wise distribution of different type of EPTB (n=89)

Gender	TB lymph node (n=57)	TB pleural effusion (n=22)	Others (n=10)
Male	23 (40.4%)	12 (54.5%)	4 (40%)
Female	34 (59.6%)	10 (45.5%)	6 (60%)

p value = 0.50

Figure 15

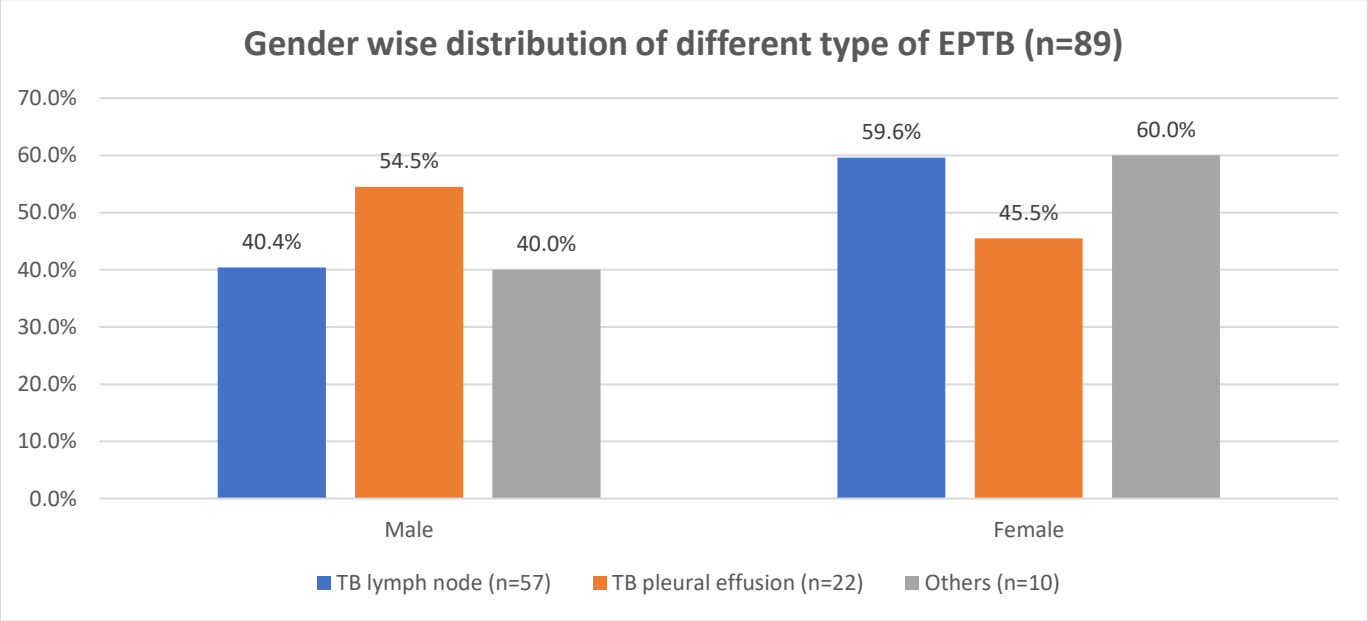


Table 15 and Fig 15 shows out of 89 cases, 23(40.4%) males and 34(59.4%) females had tubercular lymphadenopathy, 12(54.5%) males and 10(45.5%) females had tubercular pleural effusion, 4(40%) males and 6(60%) females had other forms of tuberculosis.

There is no significant correlation between gender and different types of EPTB(p=0.5)

Table 16: Symptoms in different type of EPTB (n=89)

Symptoms	TB lymph node (n=57)	TB pleural effusion (n=22)	Others (n=10)	P value
Fever	56 (98.2%)	18 (81.8%)	10 (100%)	**0.01**
Loss of appetite	55 (96.5%)	20 (90.9%)	10 (100%)	0.43
Loss of weight	55 (96.5%)	20 (90.9%)	10 (100%)	0.43

Fever was less common in subjects with TB pleural effusion compared to other types of TB.

This difference was found statistically significant (p value = 0.01)

Figure 16

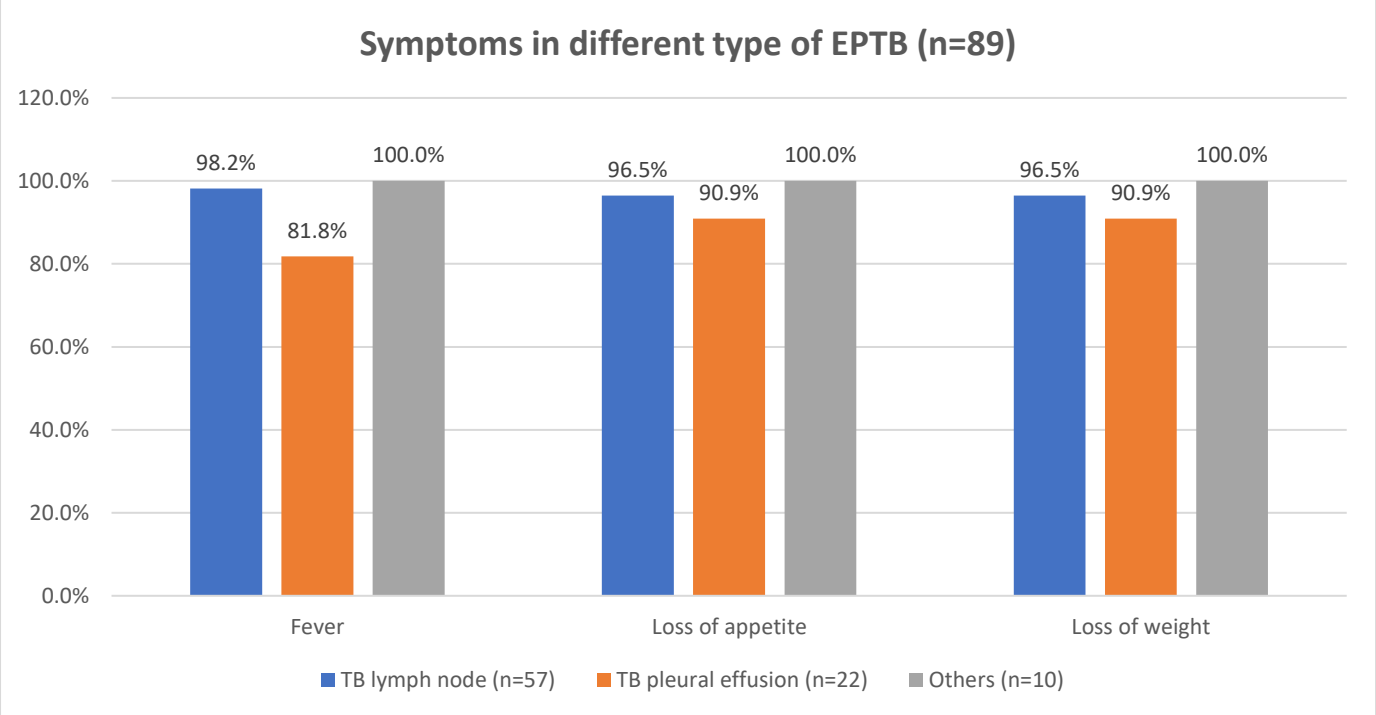


Table 17: Past history in different type of EPTB (n=89)

	TB lymph node (n=57)	TB pleural effusion (n=22)	Others (n=10)	P value
Past history of TB	7 (12.3%)	7 (31.8%)	1 (10%)	0.09
H/o defaulter/irregular intake of treatment	1 (1.8%)	5 (22.7%)	0	**<0.01**
h/o contact with TB	18 (31.6%)	8 (36.4%)	4 (40%)	0.83

H/o defaulter/irregular intake of treatment was more commonly seen in subjects with TB pleural effusion (22.7%) compared to TB lymph nodes 1.8%) or other types of TB (0%).

This difference was found statistically significant (p value< 0.01)

Figure 17

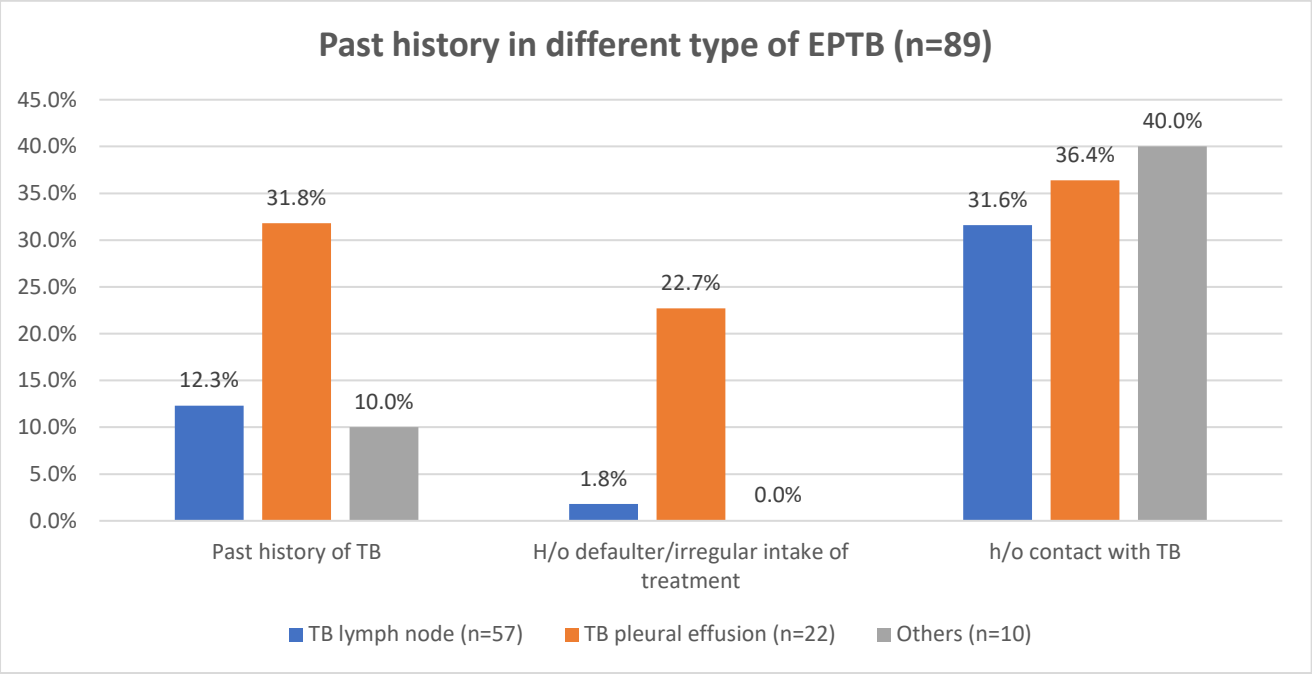


Table 18: Anthropometric profile in different type of EPTB (n=89)

	TB lymph node (n=57)	TB pleural effusion (n=22)	Others (n=10)	P value
Height				
150-160 cm	38 (66.7%)	12 (54.5%)	7 (70%)	0.55
161-180 cm	19 (33.3%)	10 (45.5%)	3 (30%)	
Weight				
40-60 kgs	39 (68.4%)	12 (54.5%)	6 (60%)	0.49
61-80 kgs	18 (31.6%)	10 (45.5%)	4 (40%)	
BMI				
Normal	38 (66.7%)	13 (59.1%)	9 (90%)	0.22
Underweight	19 (33.3%)	9 (40.9%)	1 (10%)	

Figure 18

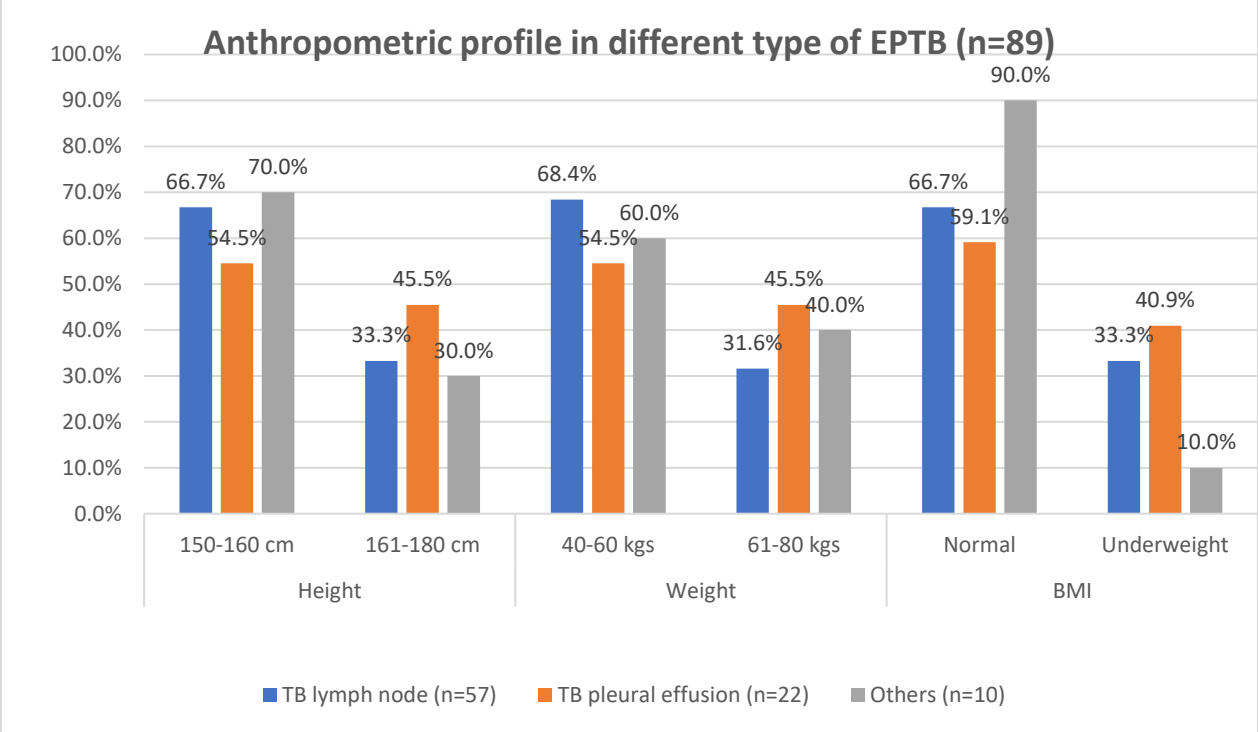


Table 19: CBNAAT finding in different type of EPTB (n=89)

CBNAAT finding	TB lymph node (n=57)	TB pleural effusion (n=22)	Others (n=10)	P value
Not detected	33 (57.9%)	21 (95.5%)	2 (20%)	**0.001**
Detected with rifampicin sensitivity	22 (38.6%)	1 (4.5%)	8 (80%)	
Detected with rifampicin resistance	2 (3.5%)	0	0	

On CBNAAT finding, detection rate was significantly lesser in subjects with TB pleural effusion (4.5%) compared to TB lymph nodes (42.1%) or other types of TB (80%).

Figure 19

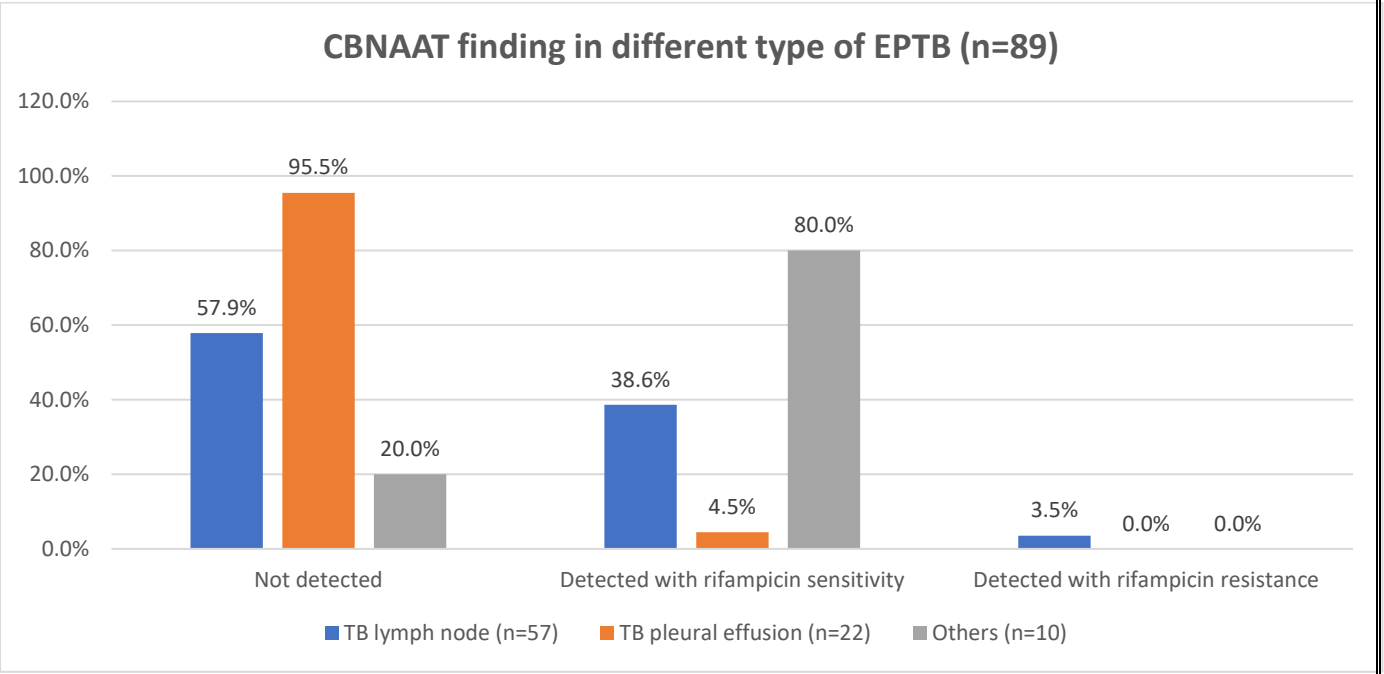
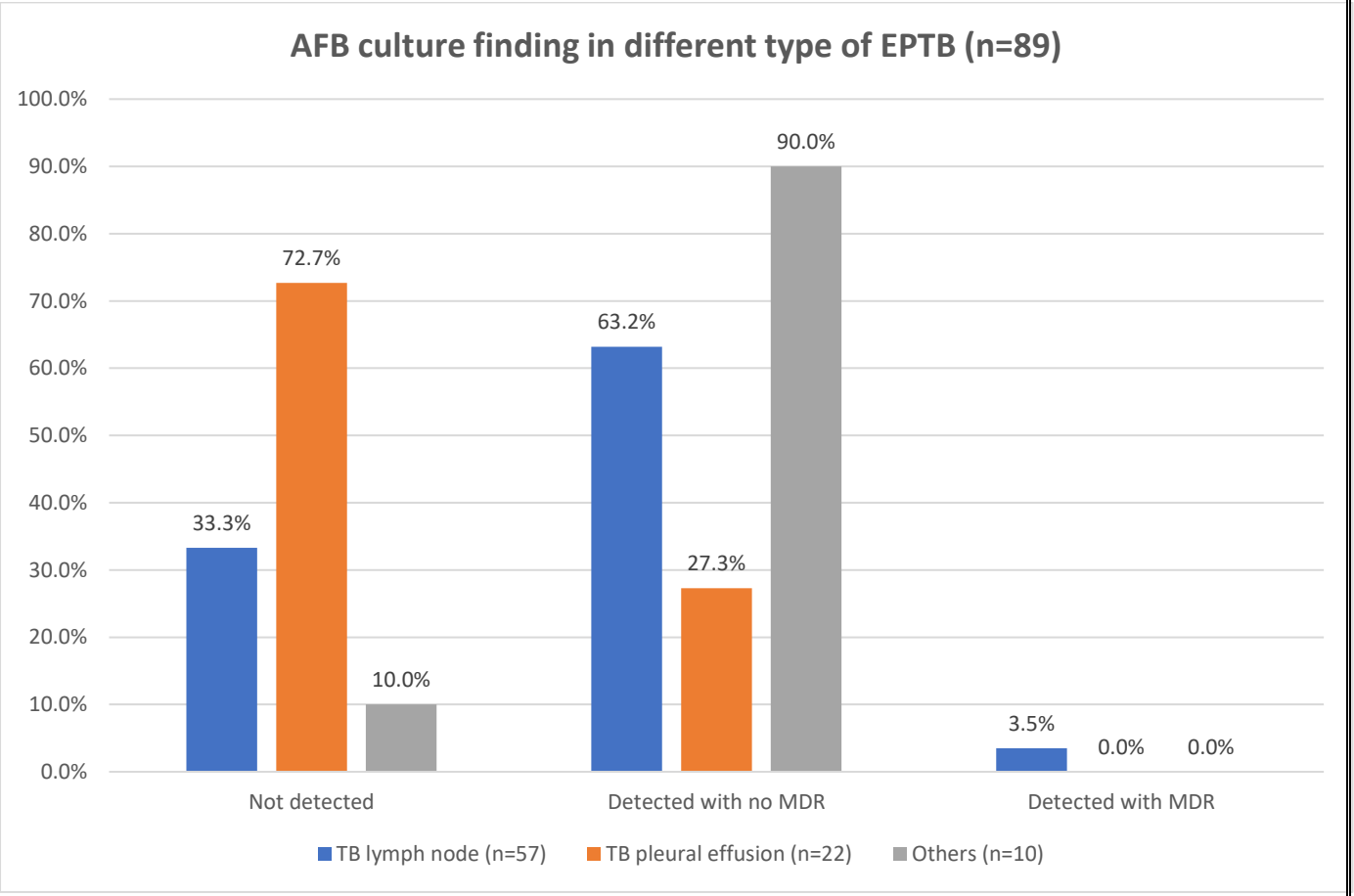


Table 20: AFB culture finding in different type of EPTB (n=89)

AFB culture	TB lymph node (n=57)	TB pleural effusion (n=22)	Others (n=10)	P value
Not detected	19 (33.3%)	16 (72.7%)	1 (10%)	**0.004**
Detected with no MDR	36 (63.2%)	6 (27.3%)	9 (90%)	
Detected with MDR	2 (3.5%)	0	0	

On AFB culture, detection rate was significantly lesser in subjects with TB pleural effusion (27.3%) compared to TB lymph nodes (66.7%) or other types of TB (90%).

Figure 20



3. **Comparison of CBNAAT and AFB culture in all forms of EPTB**

Table 21: Association of AFB culture and CBNAAT finding (n=89)

		AFB CULTURE			Total
		Not detected	Detected without MDR	Detected with MDR	
CBNAAT	Not detected	33	22	0	55
	Detected with rifampicin sensitivity	3	29	0	32
	Detected with rifampicin resistance	0	0	2	2
Total		36	51	2	89

Kappa value = 0.48; p value <0.01

There was statistically significant weak agreement seen between CBNAAT finding and AFB culture finding (Kappa value = 0.48; p value <0.01).

Figure 21

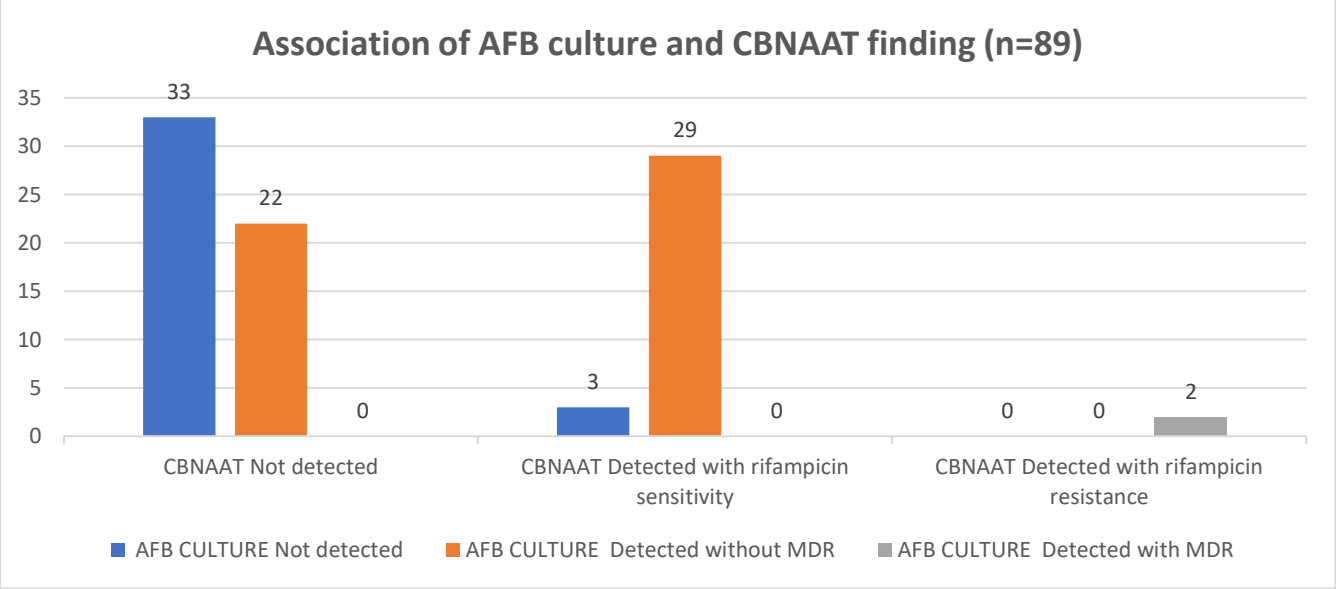


Table 22: Diagnostic accuracy of CBNAAT in detection of Extrapulmonary TB

	%	95% CI
Sensitivity	58.49%	44.13% to 71.86%
Specificity	91.67%	77.53% to 98.25%
Positive Predictive Value	91.18%	77.35% to 96.90%
Negative Predictive Value	60.00%	51.78% to 67.70%
Accuracy	71.91%	61.38% to 80.93%

Figure 22

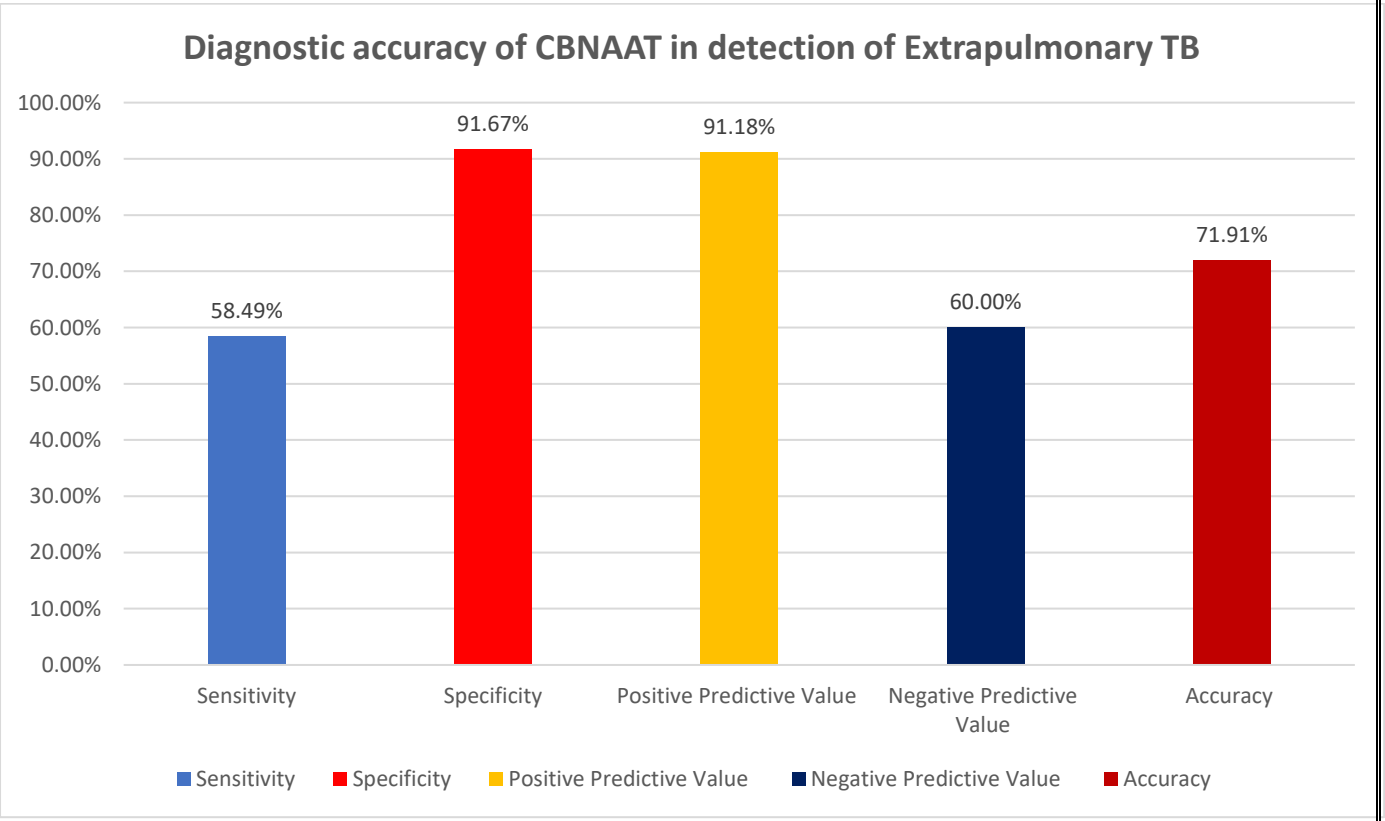


Table 23: Diagnostic accuracy of CBNAAT in different type of EPTB

	TB lymph node (n=57)	TB pleural effusion (n=22)	Others (n=10)
Sensitivity	55.26% (38.3-71.38%)	16.67% (0.42-64.12)	88.89% (51.75-99.72)
Specificity	84.21% (60.42-96.62%)	100% (79.41-100%)	100% (2.5-100%)
Positive Predictive Value	87.5% (70.45-95.36%)	100%	100%
Negative Predictive Value	48.48% (38.6-58.49%)	76.19% (69.11-82.07%)	50% (13.61-86.39%)
Accuracy	64.91% (51.13-77.09%)	77.27% (54.62-92.18%)	90% (55.5-99.75%)

Figure 23

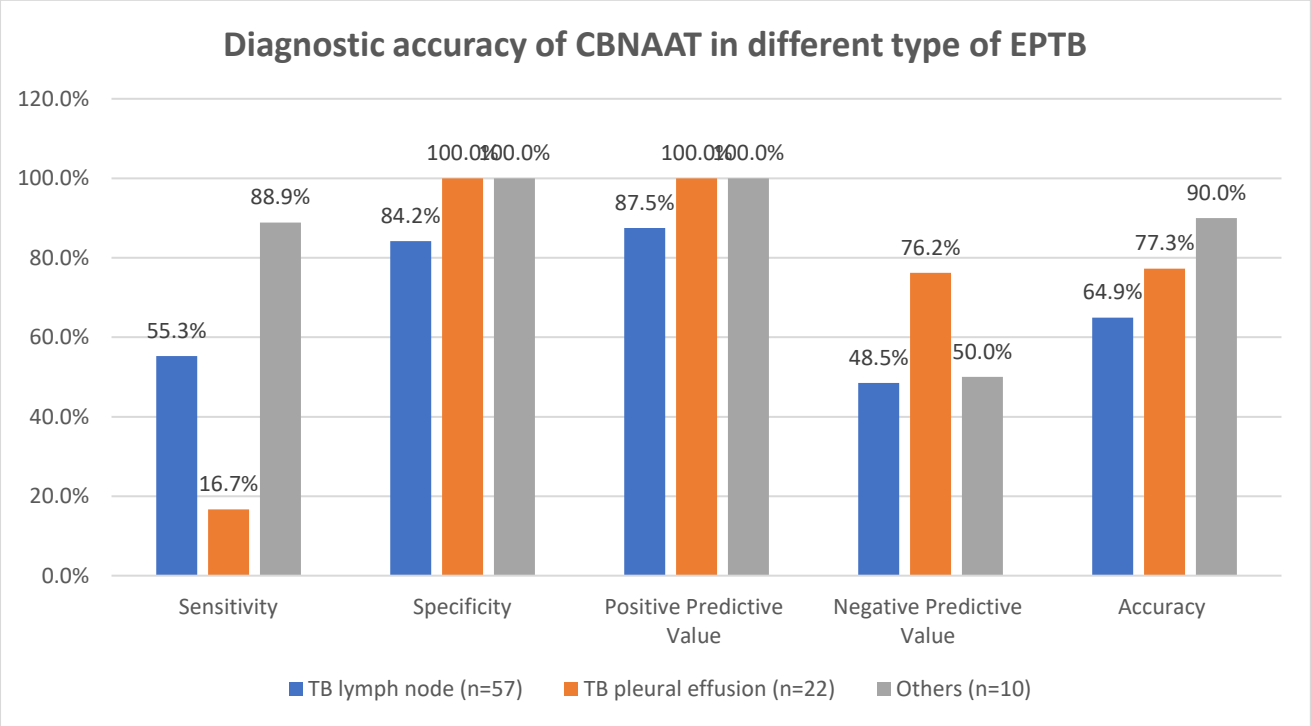
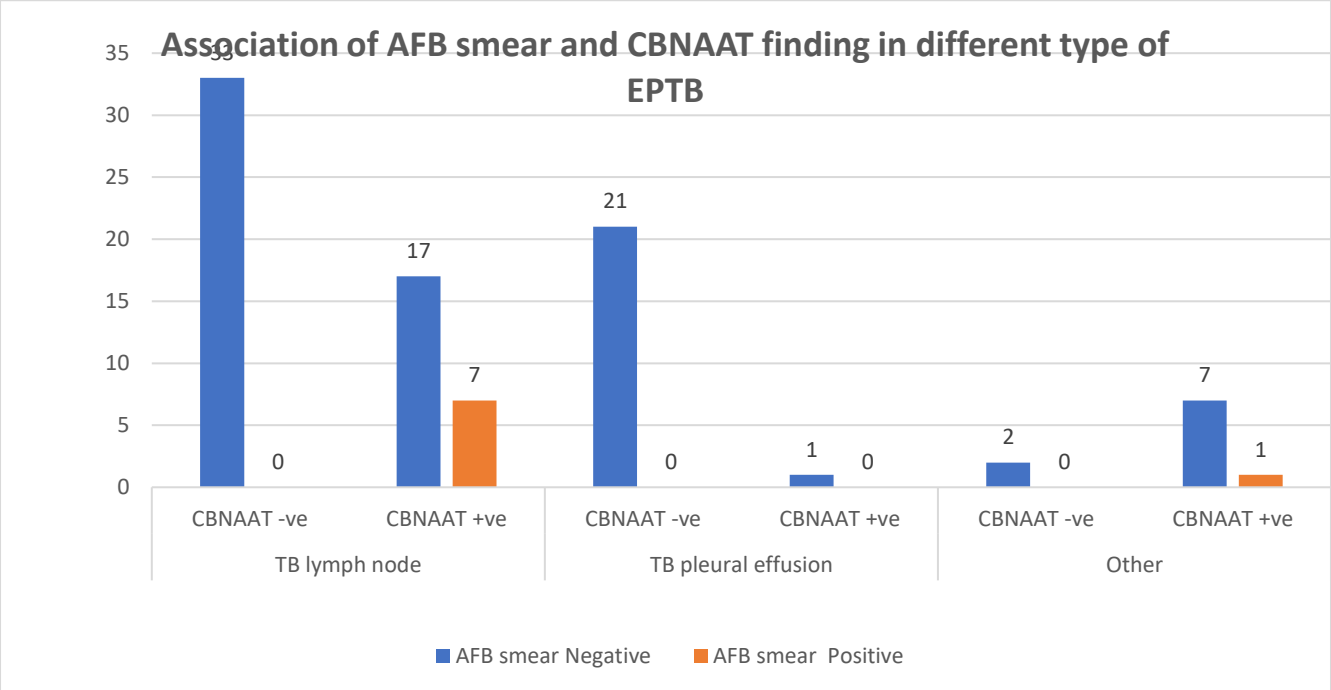


Table 24: Association of AFB smear and CBNAAT finding in different type of EPTB

		AFB smear		P value
		AFB smear Negative	AFB smear Positive	
TB lymph node	CBNAAT -ve	33	0	<0.001
	CBNAAT +ve	17	7	
TB pleural effusion	CBNAAT -ve	21	0	-
	CBNAAT +ve	1	0	
Other	CBNAAT -ve	2	0	1.0
	CBNAAT +ve	7	1	

There was significant association between CBNAAT finding and AFB smear finding in subjects with TB lymph nodes (p value <0.01).

Figure 24



DISCUSSION

This cross-sectional study was conducted in a sample size of 89 patients attending the outpatient department in a tertiary care center in the Department of Respiratory Medicine at Santosh Hospital, Ghaziabad who were clinically suspected cases of Extra Pulmonary Tuberculosis.

The study was conducted to know the yield of CBNAAT in Extra Pulmonary Tuberculosis in the locality and to compare it with AFB culture sensitivity taking it as the Gold Standard in the diagnosis of Tuberculosis.

Fever was less common in subjects with TB pleural effusion compared to other types of TB. This difference was found statistically significant (p value = 0.01)

H/o defaulter/irregular intake of treatment was more commonly seen in subjects with TB pleural effusion (22.7%) compared to TB lymph nodes 1.8%) or other types of TB (0%). This difference was found statistically significant (p value< 0.01)

Study conducted by Singh KG et al had a diagnostic yield of 77.9% in CBNAAT in tubercular peripheral lymphadenopathy.[1]

Study conducted by Shamma Shetye et al had maximum diagnostic yield of CBNAAT in pus and aspirates where 48.38 % were MTB positive with Rifampicin resistance and 49.74% were MTB positive with Rifampicin sensitive.[3]

E. Tortoli et al conducted a study in which the overall sensitivity and specificity of Xpert in Extrapulmonary Tuberculosis was 70% and 97.3%.[4]

In a study conducted by Yadav.K and Veena.M, yield of CBNAAT was 23.8% in which maximun cases of MTB positives were found in the FNAC that is 52.2%[11].

In a study conducted by Doris Hilleman on EPTB, out of 28 culture positive tissue samples, 20 came out to be positive for CBNAAT.[14]

Anu Shree Chakraborty et al conducted a study on EPTB in which the yield of CBNAAT came out to be 32%.[13]

In our study, on CBNAAT finding, detection rate was significantly lesser in subjects with TB pleural effusion (4.5%) compared to TB lymph nodes (42.1%) or other types of TB (80%) and on AFB culture, detection rate was significantly lesser in subjects with TB pleural effusion (27.3%) compared to TB lymph nodes (66.7%) or other types of TB (90%) where the other forms of EPTB samples

included ascitic fluid, pus from abscess and CSF and there was statistically significant weak agreement seen between CBNAAT finding and AFB culture finding (Kappa value = 0.48; p value <0.01).

SUMMARY

The current study was conducted in the Department of Respiratory Medicine, Santosh Hospital to study the yield of CBNAAT in EPTB and to compare the diagnostic efficacy of CBNAAT with AFB culture in all the forms of EPTB.

Out of 89 subjects included in the study who were EPTB suspects, all the extrapulmonary samples from the respective Extrapulmonary sites were subjected to CBNAAT and AFB culture, out of which 33 came out to be CBNAAT positive giving it a yield of 37% and 53 came out to be AFB culture positive giving AFB culture a yield of 59.5%.

CONCLUSION

Yield of CBNAAT in clinically suspected cases of EPTB is 37%.

Yield of AFB culture in clinically suspected cases of EPTB is 59.5%.

There was statistically significant agreement seen between CBNAAT finding and AFB culture finding.

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INFORMED CONSENT

Name of the patient: Age:

Address: Phone Number:

S.NO: Date:

I have been explained the details of the study entitled **"To study the Role of CBNAAT in Extrapulmonary Tuberculosis** "and my questions regarding the study have been answered to my satisfaction in a language understood by me.

1. I understand that I have the right to withdraw from the study at any time and to decline to answer any particular question.
2. I understand that my participation in this study is confidential and that no material that could identify me will be used in the analysis and in any reports based on this study.

I hereby provide my consent in the study entitled **"To study the Role of CBNAAT in Extrapulmonary Tuberculosis"**

Signature/ thumb impression of the patient

Signature/ thumb impression of witness

सहभागी सुचित सहमति प्र पत्र

गाइड का नाम: -

रोगी का नाम: आयु: -

पता: -

फ़ोन **नंबर**: -

एसएनओ:

मुझे अध्ययन के विवरण समझाया गया है **"To study the Role of CBNAAT in Extrapulmonary Tuberculosis"** मेरा अध्ययन के बारे में प्रश्नों को एक मेरे द्वारा समझा भाषा में मेरी संतुष्टि का उत्तर दिया गया

1. मैं समझता हूं कि मुझे किसी भी समय अध्ययन से वापस लेने का अधिकार है और किसी विशेष प्रश्न का उत्तर देने में गिरावट आई है।

2. मैं समझता हूं कि इस अध्ययन में मेरी भागी दारी गोपनीय है और सामग्री जो मुझे पहचान सकती है और रिपोर्ट इस अध्ययन के आधार पर किसी भी में विश्लेषण उपयोग नहीं की जाएगी। मैं इस प्रकार अध्ययन में अपनी सहमति प्रदान करता हूं "**To study the Role of CBNAAT in Extrapulmonary Tuberculosis**"

रोगी के हस्ताक्षर / अंगूठे की छाप _____

गवाह के हस्ताक्षर / अंगूठे की छाप

PATIENT INFORMATION SHEET

NAME:

AGE:

ADDRESS:

REGISTRATION NUMBER:

OCCUPATION:

PHONE NUMBER:

CHIEF COMPLAINTS

CASE PERFORMA

Name: Age: Regn. No.

Education Occupation

Address

Tel./ Mob. No.

CLINICAL DETAILS.

Complaints:

Medical/ Surgical History:

FIRST VISIT

PHYSICAL EXAMINATION:

Temp PR BP

Pallor	Icterus	Cyanosis
Clubbing	Lymphadenopathy	
Edema	Height	Wt.

Respiratory System

CVS

CNS

INVESTIGATION

SAMPLE FROM THE RESPECTIVE EXTRAPULMONARY SITE

CBNAAT

CULTURE

DIAGNOSIS:

TREATMENT:

CODES

NAME

AGE

18-30:1

31-50:2

51-70:3

71 and Above:4

GENDER

Male:1

Female:2

Transgender:3

TYPE OF EPTB

Tubercular lymphadenopathy:1

Tubercular pleural effusion:2

Tubercular ascites:3

Tubercular abscess:4

Tubercular meningitis:5

DURATION OF SYMPTOMS OF EPTB IN DAYS

1-15:1

16-30:2

>30:3

FEVER

High grade:1

Low grade:2

Moderate grade:3

No fever:4

LOSS OF APPETITE

Yes:1

No:0

LOSS OF WEIGHT

Yes:1

No:0

PAST H/O TB/ MDR TB

Yes, without mdr:1

Yes, with mdr:2

No:0

H/O DEFAULTER/IRREGULAR INTAKE OF TREATMENT

Yes:1

No:0

No h/o TB :3

FAMILY H/O TB/MDR TB

Yes, without mdr:1

Yes with mdr:2

No:0

H/O SMOKING

Yes:1

No:0

H/O ALCOHOL INTAKE

Yes:1

No:0

H/O DIABETES MELLITUS

Yes:1

No:0

H/O HIV

Ye:1

No:0

PALLOR

Yes:1

No:0

ICTERUS

Yes:1

No:0

CYANOSIS

Yes:1

No:0

CLUBBING

Yes:1

No:0

LYMPHADENOPATHY

Yes:1

No:0

EDEMA

Yes:1

No:0

HEART RATE

60-100:0

Bradycardia:1

Tachycardia:2

TEMPERATURE

Normal:0

High grade:1

Low grade:2

BLOOD PRESSURE

Normotensive:0

Hypotensive:1

Hypertensive:2

RESPIRATORY RATE

Normal rate:0

Bradypnoea:1

Tachypnoea:2

HEIGHT IN CMS

140-160:0

161-180:1

>180:2

WEIGHT IN KGS

40-60:0

61-80:1

>80:2

BMI

Normal:0

Underweight:1

Overweight:2

AFB DIRECT SMEAR

Mtb detected:1

Mtb not detected:0

CBNAAT

Not detected:0

Detected with rifampicin sensitivity:1

Detected with rifampicin resistance:2

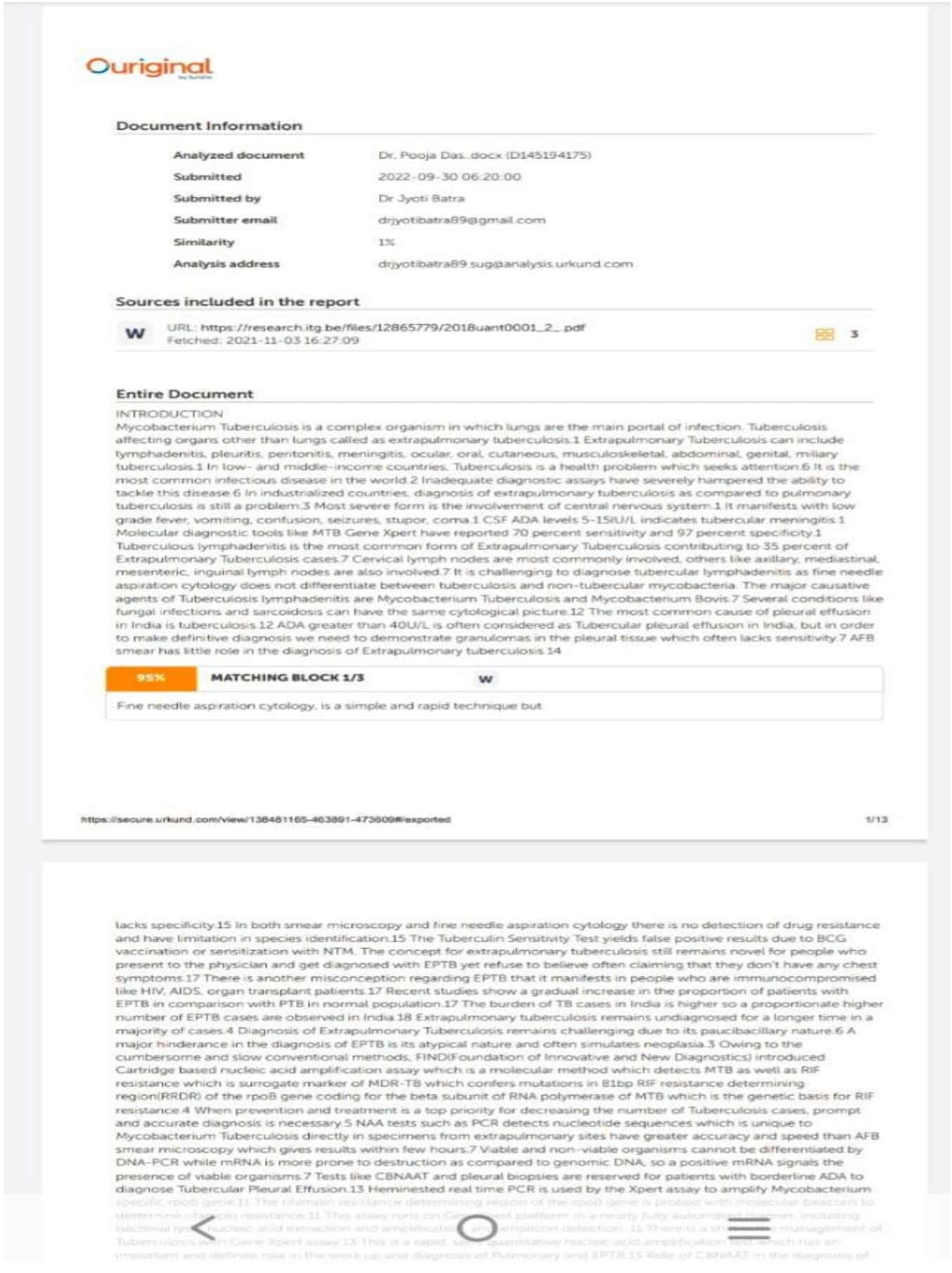
AFB CULTURE

Not Detected:0

Detected with no MDR:1

Detected with MDR:2

PLAGIARISM CERTIFICATE



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INTRODUCTION
Mycobacterium Tuberculosis is a complex organism in which lungs are the main portal of infection. Tuberculosis affecting organs other than lungs called as extrapulmonary tuberculosis.1 Extrapulmonary Tuberculosis can include lymphadenitis, pleuritis, peritonitis, meningitis, ocular, oral, cutaneous, musculoskeletal, abdominal, genital, miliary tuberculosis.1 In low- and middle-income countries, Tuberculosis is a health problem which seeks attention.6 It is the most common infectious disease in the world.2 Inadequate diagnostic assays have severely hampered the ability to tackle this disease.6 In industrialized countries, diagnosis of extrapulmonary tuberculosis as compared to pulmonary tuberculosis is still a problem.3 Most severe form is the involvement of central nervous system.1 It manifests with low grade fever, vomiting, confusion, seizures, stupor, coma.1 CSF ADA levels 5-15IU/L indicates tubercular meningitis.1 Molecular diagnostic tools like MTB Gene Xpert have reported 70 percent sensitivity and 97 percent specificity.1 Tuberculous lymphadenitis is the most common form of Extrapulmonary Tuberculosis contributing to 35 percent of Extrapulmonary Tuberculosis cases.7 Cervical lymph nodes are most commonly involved, others like axillary, mediastinal, mesenteric, inguinal lymph nodes are also involved.7 It is challenging to diagnose tubercular lymphadenitis as fine needle aspiration cytology does not differentiate between tuberculosis and non-tubercular mycobacteria. The major causative agents of Tuberculosis lymphadenitis are Mycobacterium Tuberculosis and Mycobacterium Bovis.7 Several conditions like fungal infections and sarcoidosis can have the same cytological picture.12 The most common cause of pleural effusion in India is tuberculosis.12 ADA greater than 40U/L is often considered as Tubercular pleural effusion in India, but in order to make definitive diagnosis we need to demonstrate granulomas in the pleural tissue which often lacks sensitivity.7 AFB smear has little role in the diagnosis of Extrapulmonary tuberculosis.14

95% MATCHING BLOCK 1/3 W

Fine needle aspiration cytology, is a simple and rapid technique but

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lacks specificity.15 In both smear microscopy and fine needle aspiration cytology there is no detection of drug resistance and have limitation in species identification.15 The Tuberculin Sensitivity Test yields false positive results due to BCG vaccination or sensitization with NTM. The concept for extrapulmonary tuberculosis still remains novel for people who present to the physician and get diagnosed with EPTB yet refuse to believe often claiming that they don't have any chest symptoms.17 There is another misconception regarding EPTB that it manifests in people who are immunocompromised like HIV, AIDS, organ transplant patients.17 Recent studies show a gradual increase in the proportion of patients with EPTB in comparison with PTB in normal population.17 The burden of TB cases in India is higher so a proportionate higher number of EPTB cases are observed in India.18 Extrapulmonary tuberculosis remains undiagnosed for a longer time in a majority of cases.4 Diagnosis of Extrapulmonary Tuberculosis remains challenging due to its paucibacillary nature.6 A major hinderance in the diagnosis of EPTB is its atypical nature and often simulates neoplasia.3 Owing to the cumbersome and slow conventional methods, FIND(Foundation of Innovative and New Diagnostics) introduced Cartridge based nucleic acid amplification assay which is a molecular method which detects MTB as well as RIF resistance which is surrogate marker of MDR-TB which confers mutations in 81bp RIF resistance determining region(RRDR) of the rpoB gene coding for the beta subunit of RNA polymerase of MTB which is the genetic basis for RIF resistance.4 When prevention and treatment is a top priority for decreasing the number of Tuberculosis cases, prompt and accurate diagnosis is necessary.5 NAA tests such as PCR detects nucleotide sequences which is unique to Mycobacterium Tuberculosis directly in specimens from extrapulmonary sites have greater accuracy and speed than AFB smear microscopy which gives results within few hours.7 Viable and non-viable organisms cannot be differentiated by DNA-PCR while mRNA is more prone to destruction as compared to genomic DNA, so a positive mRNA signals the presence of viable organisms.7 Tests like CBNAAT and pleural biopsies are reserved for patients with borderline ADA to diagnose Tubercular Pleural Effusion.13 Heminested real time PCR is used by the Xpert assay to amplify Mycobacterium specific rpoB gene.11 The rifampin resistance determining region of the rpoB gene is probed with molecular beacons to determine rifampin resistance.11 This assay runs on GeneXpert platform in a nearly fully automated manner, including bacterial lysis, nucleic acid extraction and amplification and amplicon detection. 11 There is a strong need for management of Tuberculosis with Gene Xpert assay.13 This is a rapid, semi-quantitative nucleic acid amplification test which has an important and definite role in the work up and diagnosis of Pulmonary and EPTB.13 Role of CBNAAT in the diagnosis of